

Supplementary Information 1

Materials and Methods

Western Blotting

Cells or sEVs were lysed by the radioimmunoprecipitation assay (RIPA) lysis buffer (Beyotime, Shanghai, China) with inhibitors of protease and phosphatase. Protein samples were separated by sodium dodecyl sulfate-polyacrylamide gel (SDS-PAGE) electrophoresis and transferred onto polyvinylidene difluoride (PVDF) membranes (EMD Millipore, Billerica, MA, USA). The PVDF membranes were blocked with 5% bovine serum albumin for 1 h, and incubated with primary antibodies at 4°C for 10 h. After incubation with horseradish peroxidase-labeled secondary antibodies for 1 h, the PVDF membranes were developed by Electro-Chemi-Luminescence (ECL) detection reagent (Biosharp, Hefei, China). The integrated density of the gray value for each WB band was analyzed by the ImageJ Software (Bethesda, MD, USA). The density ratios of target proteins and β -Actin were calculated, and the relative expression quantities of control groups were normalized to 1. The primary antibodies used in this study are listed in Table S1.

Quantitative Real-Time PCR Analysis

After treatments, RNA was extracted from NPCs by the RNA-easy Isolation Reagent (Vazyme Biotech, Nanjing, China). The RNA concentration and purity were assessed using the Nanodrop 2000. The mRNA was reverse-transcribed by complementary DNA (cDNA) Synthesis Kit (Yeasen Biotechnology, Shanghai, China). The gene expression levels were

quantified by qPCR SYBR Green Master Mix (Yeastar Biotechnology) on the Step One Plus Real-Time PCR system (Bio-Rad, Hercules, CA, USA). Relative quantities of target genes were normalized to *Actb* levels and calculated using the $2^{-\Delta\Delta C_t}$ method ¹. $2^{-\Delta\Delta C_t} > 1$ indicated that the expression of the target gene in the treatment group was more abundant than that in the corresponding control group. The primer sequences are listed in Table S2.

Histological Analysis

The paraffin-embedded rat IVD samples were cut into 4 μ m thick sections. Hematoxylin and eosin (HE) and safranin O-fast green (SOFG) were conducted to assess histological scoring as previously reported ².

Immunohistochemical (IHC) staining was conducted to detect the ratios of senescent NPCs, and the expression levels of SASP and LIN28A in rat IVD tissues. The paraffin sections were deparaffinized, rehydrated, and treated with 3% H₂O₂ for 20 min at room temperature. Antigen retrieval was conducted in EDTA buffer (pH 8.0) at 95°C for 15 min. Subsequently, the sections were blocked with 20% goat serum at room temperature for 1 h, followed by the incubation with anti-p16 (1:500), anti-IL-1 β (1:300), anti-TNF- α (1:300), anti-MMP13 (1:250), and anti-LIN28A (1:200) antibodies at 4°C overnight. Nonimmune rabbit IgG was used as negative control primary antibody. After being washed, the sections were incubated with horseradish peroxidase-conjugated secondary antibody at room temperature for 1 h, visualized with diaminobenzidine, and stained with hematoxylin. The IHC Intensity was measured by ImageJ as previously reported ³.

References

1. Schmittgen TD, Livak KJ. Analyzing real-time PCR data by the comparative C(T) method.
Nat Protoc. 2008;3(6):1101-1108. doi: 10.1038/nprot.2008.73
2. Rutges JP, Duit RA, Kummer JA, et al. A validated new histological classification for
intervertebral disc degeneration. *Osteoarthritis Cartilage.* 2013;21(12):2039-2047. doi:
10.1016/j.joca.2013.10.001
3. Jensen EC. Quantitative analysis of histological staining and fluorescence using ImageJ.
Anat Rec (Hoboken). 2013;296(3):378-381. doi: 10.1002/ar.22641

Supplementary Tables

Table S1 The antibodies used in the study

Antibodies	Source	Catalog No.	Applications
anti-rat CD32	BD, Franklin Lake, NJ	550270	FCM
FITC-conjugated anti-rat CD11b/c	BioLegend, San Diego, CA	201805	FCM
APC-conjugated anti-rat CD68	Miltenyi, Bergesch Gladbach, Germany	130-102-725	FCM
BV421-conjugated anti-rat CD86	BD	743211	FCM
PE-conjugated anti-CD206	Santa Cruz, Dallas, TX	sc-58986 PE	FCM
β -Actin	Affinity, Cincinnati, OH	AF7018	WB
NLRP3	Abmart, Shanghai, China	T55651	WB
NF- κ B p65	Abmart	T55034	WB
p-NF- κ B p65 (S536)	Abmart	TP56372	WB
STAT3	Abclonal, Wuhan, China	A1192	WB
p-STAT3 (Y705)	Abclonal	AP0070	WB
TSG101	Abclonal	A5789	WB
CD9	Abclonal	A1703	WB
CD63	Abclonal	A19023	WB
CD81	Abclonal	A5270	WB
p16 (INK4A/CDKN2A)	Proteintech, Rosemont, IL	10883-1-AP	WB, IHC
p21 (CDKN1A)	Santa Cruz	sc-6246	WB
p53	Santa Cruz	sc-98	WB

Collagen II	Affinity	AF0135	WB
SOX9	Abclonal	A2479	WB
MMP13	Proteintech	18165-1-AP	WB, IHC
IL-1 β	Abclonal	A16288	IHC
TNF- α	Abclonal	A0277	IHC
LIN28A	Abcam, Cambridge, UK	ab279647	WB, IHC

FCM: Flow cytometry; WB: Western blotting; IHC: Immunohistochemical staining

Table S2 The primer sequences for qRT-PCR used in the study

Primer	Sequences (5' to 3')
<i>Actb</i> -F	CGTTGACATCCGTAAAGACCTC
<i>Actb</i> -R	TAGGAGCCAGGGCAGTAATCT
<i>Il1a</i> -F	CCTCGTCCTAAGTCACTCGC
<i>Il1a</i> -R	GCAGAGTCTTTTTGACCCTCCT
<i>Il1b</i> -F	GGTGGTTCAAGGCATAACA
<i>Il1b</i> -R	TGTCGAGATGCTGCTGTGAG
<i>Il6</i> -F	GACCAAGACCATCCAAC
<i>Il6</i> -R	TAGGTTTGCCGAGTAGAC
<i>Ccl2</i> -F	ATGCAGTTAATGCCCCACTC
<i>Ccl2</i> -R	TTCCTTATTGGGGTCAGCAC
<i>Ccl5</i> -F	ATATGGCTCGGACACCACTC
<i>Ccl5</i> -R	CAAAGACGACTGCAAGGTTGG
<i>Tnf</i> -F	CCAATCTGTGTCCTTCTAA
<i>Tnf</i> -R	TTCTGAGCATCGTAGTTG
<i>Mmp3</i> -F	TTTGGCCGTCTCTTCCATCC
<i>Mmp3</i> -R	GCATCGATCTTCTGGACGGT
<i>Mmp13</i> -F	GGA CTCACTGTTGGTCCCTG
<i>Mmp13</i> -R	GGATTCCCGCAAGAGTCACA
<i>Col2a1</i> -F	CTCAAGTCGCTGAACAACCA
<i>Col2a1</i> -R	GTCTCCGCTCTTCCACTCTG

<i>Acan</i> -F	AAGTGCTATGCTGGCTGGTT
<i>Acan</i> -R	GGTCTGGTTGGGGTAGAGGT
<i>Lin28a</i> -F	AGAAAGTGGGAATCGGGTGG
<i>Lin28a</i> -R	CTACAGAAGGGCTTCTCCCCT
<i>Tmsb4x</i> -F	TTCCACGAGCATTGCCTTC
<i>Tmsb4x</i> -R	GCCTTCCTGGTCAGTAGTTC
<i>Tmsb10</i> -F	AGAAAACCGAGACGCAGGAG
<i>Tmsb10</i> -R	CACATCACGAGGGGGTTCTT
<i>Ptma</i> -F	ATGACATGCGCTCTTCACCA
<i>Ptma</i> -R	TTCACACATACATCAAACAGGC
<i>U6</i> -RT	AACGCTTCACGAATTTGCGT
<i>U6</i> -F	CTCGCTTCGGCAGCACA
<i>U6</i> -R	AACGCTTCACGAATTTGCGT
<i>let-7i-5p</i> -RT	CTCAACTGGTGTCGTGGAGTCGGCAATTCAGTTGAGAACAGCAC
<i>let-7i-5p</i> -F	ACACTCCAGCTGGGTGAGGTAGTAGTTT
<i>let-7i-5p</i> -R	TGGTGTCGTGGAGTCG

F: Forward primer; R: Reverse primer; RT: Reverse transcription primer

Table S3 The siRNA sequences of *Lin28a*

siRNA	Sequences (5' to 3')
si- <i>Lin28a</i> -1-sense	GCAUCUGUAAGUGGUUCAA
si- <i>Lin28a</i> -1-antisense	UUGAACCACUUACAGAUGC
si- <i>Lin28a</i> -2-sense	GAGCAAGCUGCACAUGGAA
si- <i>Lin28a</i> -2-antisense	UUCCAUGUGCAGCUUGCUC
si- <i>Lin28a</i> -3-sense	GCCAAAGCAUCAGCCAUAU
si- <i>Lin28a</i> -3-antisense	AUAUGGCUGAUGCUUUGGC

Table S4: RNA-seq results of rat BMDMs

Table S5 Inflammatory factor concentrations in MΦ-CM detected by CBA

Treatment	CCL2	TNF-α	IL-1β	IL-1α	IL-6
	(pg/ml)	(pg/ml)	(pg/ml)	(pg/ml)	(pg/ml)
Untreated MΦ 1	1928.88	10.15	<8.73	<8.05	<70.21
Untreated MΦ 2	1414.58	<7.43	10.05	<8.05	<70.21
Untreated MΦ 3	2847.78	10.15	<8.73	<8.05	<70.21
Untreated MΦ 4	2813.82	9.61	<8.73	<8.05	<70.21
Untreated MΦ 5	2013.42	8.43	<8.73	<8.05	<70.21
LPS+IFNγ-MΦ 1	15189.42	698.34	<8.73	144.85	1595.94
LPS+IFNγ-MΦ 2	20654.21	451.91	<8.73	58.16	1179.01
LPS+IFNγ-MΦ 3	20913.73	601.97	<8.73	110.71	1291.42
LPS+IFNγ-MΦ 4	25072.79	818.14	9.32	175.10	2304.05
LPS+IFNγ-MΦ 5	9697.95	25.55	11.05	24.85	1463.05
IL-4-MΦ 1	4828.81	7.49	<8.73	<8.05	<70.21
IL-4-MΦ 2	3279.93	<7.43	<8.73	<8.05	<70.21
IL-4-MΦ 3	4022.96	<7.43	<8.73	<8.05	<70.21
IL-4-MΦ 4	5412.20	7.63	<8.73	<8.05	<70.21
IL-4-MΦ 5	1391.77	<7.43	<8.73	<8.05	<70.21

Table S6 Inflammatory factor concentrations in NPC-CM detected by CBA

Treatment	CCL2 (pg/ml)	TNF-α (pg/ml)	IL-1β (pg/ml)	IL-1α (pg/ml)	IL-6 (pg/ml)
Control 1	19.16	<7.43	<8.73	<8.05	<70.21
Control 2	83.48	<7.43	<8.73	<8.05	<70.21
Control 3	94.60	<7.43	<8.73	<8.05	72.67
Control 4	178.07	<7.43	<8.73	<8.05	<70.21
Control 5	482.09	<7.43	<8.73	<8.05	<70.21
LPS+IFNγ-MΦ-CM 1	3983.14	<7.43	<8.73	<8.05	2318.71
LPS+IFNγ-MΦ-CM 2	4481.39	29.81	<8.73	17.87	15645.13
LPS+IFNγ-MΦ-CM 3	5482.73	645.99	<8.73	<8.05	21567.77
LPS+IFNγ-MΦ-CM 4	5717.86	12.23	<8.73	<8.05	7474.44
LPS+IFNγ-MΦ-CM 5	9443.74	<7.43	<8.73	<8.05	1154.95
IL-4-MΦ-CM 1	574.09	<7.43	<8.73	<8.05	<70.21
IL-4-MΦ-CM 2	632.41	<7.43	<8.73	<8.05	<70.21
IL-4-MΦ-CM 3	656.10	14.06	<8.73	<8.05	78.78
IL-4-MΦ-CM 4	674.72	<7.43	<8.73	<8.05	82.07
IL-4-MΦ-CM 5	688.67	<7.43	<8.73	<8.05	145.76
LPS+IFNγ-MΦ-sEV 1	5055.00	<7.43	<8.73	<8.05	15873.12
LPS+IFNγ-MΦ-sEV 2	5775.20	8.09	<8.73	<8.05	14469.62
LPS+IFNγ-MΦ-sEV 3	6626.00	22.12	<8.73	8.47	16265.37
LPS+IFNγ-MΦ-sEV 4	7441.52	22.42	<8.73	<8.05	8514.32

LPS+IFNγ-MΦ-sEV 5	13019.38	21.76	<8.73	<8.05	8007.16
IL-4-MΦ-sEV 1	2493.29	<7.43	<8.73	<8.05	11404.50
IL-4-MΦ-sEV 2	2580.53	<7.43	<8.73	<8.05	8480.58
IL-4-MΦ-sEV 3	4239.71	<7.43	<8.73	<8.05	11113.81
IL-4-MΦ-sEV 4	6779.95	<7.43	<8.73	<8.05	7771.55
IL-4-MΦ-sEV 5	7292.55	<7.43	<8.73	<8.05	7061.65

Table S7: PANDORA-seq results of MΦ-sEVs

miRNA	log2FoldChange	pvalue	padj	LPS+IFNγ- MΦ-sEV-1	LPS+IFNγ- MΦ-sEV-2	LPS+IFNγ- MΦ-sEV-3	IL-4-MΦ- sEV-1	IL-4-MΦ- sEV-2	IL-4-MΦ- sEV-3
rno-let-7a-1-3p	-0.86951	0.678676	0.978652	0	2	2	1	1	1
rno-let-7a-5p	-0.49911	0.516073	0.978652	20	12	61	23	48	16
rno-let-7b-5p	-0.20681	0.749231	0.978652	21	24	32	19	38	38
rno-let-7c-2-3p	-0.86951	0.678676	0.978652	0	2	2	1	1	1
rno-let-7c-5p	-0.2257	0.710337	0.978652	31	42	34	34	37	65
rno-let-7d-3p	-1.42837	0.606373	0.978652	1	2	0	2	0	0
rno-let-7d-5p	-1.75624	0.110108	0.978652	8	6	12	1	2	8
rno-let-7e-5p	0.744737	0.580382	0.978652	4	1	1	5	8	3
rno-let-7f-1-3p	2.018804	0.612547	0.978652	0	0	0	0	3	0
rno-let-7f-5p	-0.01519	0.973538	0.981664	135	191	200	244	274	242
rno-let-7g-3p	-0.00846	0.996311	0.996311	2	0	2	2	1	3
rno-let-7g-5p	-0.55907	0.306416	0.978652	40	58	58	64	32	63
rno-let-7i-3p	0.187513	0.899867	0.978652	1	2	6	0	6	7
rno-let-7i-5p	-0.19176	0.715752	0.978652	372	732	412	752	434	841
rno-miR-1-3p	-0.75869	0.510429	0.978652	1	3	17	6	4	6
rno-miR-101a-3p	0.526616	0.513311	0.978652	4	13	22	14	37	23
rno-miR-101a-5p	0.386058	0.924624	0.978652	0	0	0	0	0	1
rno-miR-101b-3p	0.393554	0.810759	0.978652	2	0	3	6	1	3
rno-miR-103-3p	-0.62275	0.469223	0.978652	5	9	16	7	8	12
rno-miR-106b-3p	1.214603	0.76394	0.978652	0	0	0	1	0	1
rno-miR-106b-5p	0.884668	0.512023	0.978652	3	1	2	4	2	11
rno-miR-107-3p	-1.09174	0.484812	0.978652	3	1	3	2	1	2

rno-miR-10a-5p	0.530746	0.772878	0.978652	0	0	6	1	6	3
rno-miR-122-5p	-1.84854	0.013208	0.792484	482	76	283	188	54	147
rno-miR-125a-3p	-4.55599	0.032629	0.978652	2	3	4	0	0	0
rno-miR-125a-5p	-1.12831	0.373363	0.978652	1	7	13	1	9	2
rno-miR-125b-2-3p	0.386058	0.924624	0.978652	0	0	0	0	1	0
rno-miR-125b-5p	-0.10764	0.936822	0.978652	0	3	32	2	29	5
rno-miR-126a-3p	-0.42291	0.583707	0.978652	289	37	457	521	192	171
rno-miR-126a-5p	-0.88128	0.304616	0.978652	98	6	116	88	29	67
rno-miR-127-3p	-0.2387	0.838862	0.978652	2	1	13	8	5	5
rno-miR-127-5p	-3.83561	0.176538	0.978652	3	0	2	0	0	0
rno-miR-128-3p	-0.50372	0.546502	0.978652	6	10	11	11	7	10
rno-miR-1298	2.087205	0.600224	0.978652	0	0	0	4	0	0
rno-miR-1306-3p	-1.5375	0.706327	0.978652	0	1	0	0	0	0
rno-miR-1306-5p	0.386058	0.924624	0.978652	0	0	0	0	1	0
rno-miR-130a-3p	0.195231	0.747181	0.978652	26	55	28	85	61	45
rno-miR-130b-3p	-0.71576	0.376776	0.978652	41	17	16	48	19	10
rno-miR-132-3p	0.386058	0.924624	0.978652	0	0	0	1	0	0
rno-miR-133a-3p	1.10075	0.78607	0.978652	0	0	0	2	0	0
rno-miR-136-3p	-0.38455	0.8536	0.978652	0	0	8	6	0	2
rno-miR-139-5p	1.053113	0.766613	0.978652	0	0	1	0	3	0
rno-miR-140-3p	-0.33357	0.634978	0.978652	17	10	34	36	16	19
rno-miR-140-5p	-0.35204	0.622055	0.978652	12	24	23	18	13	36
rno-miR-141-3p	-3.74385	0.263277	0.978652	4	0	0	0	0	0
rno-miR-142-3p	0.234579	0.649203	0.978652	230	183	229	367	252	531
rno-miR-142-5p	0.612093	0.35427	0.978652	29	200	143	294	321	182
rno-miR-144-3p	0.118369	0.930069	0.978652	2	3	6	12	0	6

rno-miR-144-5p	1.138432	0.550764	0.978652	1	1	1	10	1	0
rno-miR-145-5p	0.134066	0.905509	0.978652	5	0	16	16	7	9
rno-miR-146a-3p	1.386836	0.535814	0.978652	0	1	1	2	5	0
rno-miR-146a-5p	0.083234	0.888721	0.978652	368	757	259	1056	743	508
rno-miR-146b-3p	-0.63688	0.828519	0.978652	0	0	4	0	0	3
rno-miR-146b-5p	0.389388	0.683797	0.978652	1	9	11	9	14	14
rno-miR-147	-0.74869	0.525212	0.978652	14	11	0	12	4	10
rno-miR-148a-3p	-0.10627	0.897732	0.978652	12	4	26	13	16	25
rno-miR-148a-5p	-1.5375	0.706327	0.978652	1	0	0	0	0	0
rno-miR-148b-3p	0.622058	0.476807	0.978652	5	3	14	20	9	19
rno-miR-148b-5p	-1.5375	0.706327	0.978652	0	0	1	0	0	0
rno-miR-150-5p	0.617632	0.68933	0.978652	0	1	6	2	8	3
rno-miR-151-5p	-0.34787	0.574582	0.978652	27	22	25	41	25	24
rno-miR-152-3p	0.759854	0.369847	0.978652	6	11	8	37	21	7
rno-miR-155-5p	-3.1918	5.44E-06	0.001307	26	101	66	7	11	12
rno-miR-15b-3p	0.746247	0.567669	0.978652	2	3	1	8	3	5
rno-miR-15b-5p	-0.37291	0.635524	0.978652	25	14	10	31	10	22
rno-miR-16-5p	0.417363	0.384012	0.978652	224	248	206	643	360	411
rno-miR-17-1-3p	-0.69868	0.793611	0.978652	0	3	0	2	0	1
rno-miR-17-5p	0.056349	0.915154	0.978652	41	47	45	93	52	67
rno-miR-181a-1-3p	1.30925	0.652873	0.978652	0	1	0	2	2	0
rno-miR-181a-5p	-0.8852	0.267248	0.978652	7	12	42	11	17	15
rno-miR-181b-1-3p	0.386058	0.924624	0.978652	0	0	0	0	1	0
rno-miR-181b-5p	-0.23838	0.829569	0.978652	11	1	5	12	4	8
rno-miR-181c-3p	-1.49846	0.687437	0.978652	0	2	0	1	0	0
rno-miR-181d-5p	1.552146	0.572505	0.978652	1	0	0	3	0	2

rno-miR-182	-1.97224	0.508495	0.978652	1	0	2	0	0	1
rno-miR-183-5p	1.10075	0.78607	0.978652	0	0	0	2	0	0
rno-miR-1839-5p	-3.93105	0.156737	0.978652	2	0	4	0	0	0
rno-miR-184	-1.5375	0.706327	0.978652	0	0	1	0	0	0
rno-miR-1843a-3p	-0.57571	0.887799	0.978652	0	1	0	0	0	1
rno-miR-1843a-5p	-1.5375	0.706327	0.978652	0	1	0	0	0	0
rno-miR-1843b-5p	-1.5375	0.706327	0.978652	0	1	0	0	0	0
rno-miR-185-5p	0.133161	0.947077	0.978933	2	0	1	1	3	1
rno-miR-186-5p	-0.58549	0.439789	0.978652	12	9	33	20	20	10
rno-miR-187-3p	-0.57571	0.887799	0.978652	0	0	1	0	1	0
rno-miR-188-5p	1.798376	0.65294	0.978652	0	0	0	2	1	0
rno-miR-18a-5p	-1.62636	0.164675	0.978652	10	3	6	6	3	1
rno-miR-191a-3p	-2.35133	0.452381	0.978652	3	0	0	0	0	1
rno-miR-191a-5p	-0.49142	0.317414	0.978652	346	287	410	496	392	235
rno-miR-192-5p	-0.4477	0.887088	0.978652	2	0	0	3	0	0
rno-miR-193a-5p	1.427645	0.722876	0.978652	0	0	0	0	2	0
rno-miR-194-5p	2.271213	0.528369	0.978652	0	0	0	2	2	0
rno-miR-1949	0.386058	0.924624	0.978652	0	0	0	0	1	0
rno-miR-196b-5p	-1.5375	0.706327	0.978652	1	0	0	0	0	0
rno-miR-199a-3p	-0.62906	0.425251	0.978652	12	7	31	18	18	9
rno-miR-199a-5p	-0.62879	0.513555	0.978652	16	1	21	12	11	13
rno-miR-19a-3p	0.621543	0.420959	0.978652	4	13	10	20	18	22
rno-miR-19a-5p	-1.5375	0.706327	0.978652	0	1	0	0	0	0
rno-miR-19b-3p	0.147913	0.791072	0.978652	42	40	49	107	41	76
rno-miR-204-5p	0.386058	0.924624	0.978652	0	0	0	0	1	0
rno-miR-205	-4.55588	0.10923	0.978652	7	0	0	0	0	0

rno-miR-206-3p	-1.5375	0.706327	0.978652	1	0	0	0	0	0
rno-miR-208a-3p	-2.17089	0.592683	0.978652	0	0	2	0	0	0
rno-miR-20a-5p	-0.52429	0.531564	0.978652	5	10	18	10	7	15
rno-miR-20b-5p	-1.9352	0.330943	0.978652	2	0	6	2	0	1
rno-miR-21-3p	-1.01322	0.632822	0.978652	0	8	0	1	0	5
rno-miR-21-5p	0.107484	0.848276	0.978652	114	397	217	535	300	342
rno-miR-210-3p	-1.60722	0.041806	0.978652	13	40	13	13	11	9
rno-miR-218a-5p	-1.21847	0.542645	0.978652	0	3	2	1	1	1
rno-miR-22-3p	1.420715	0.292229	0.978652	1	6	2	4	28	1
rno-miR-22-5p	0.386058	0.924624	0.978652	0	0	0	0	1	0
rno-miR-221-3p	-0.43802	0.562493	0.978652	12	28	13	29	21	10
rno-miR-222-3p	1.757621	0.660514	0.978652	0	0	0	2	0	1
rno-miR-222-5p	0.386058	0.924624	0.978652	0	0	0	0	0	1
rno-miR-223-3p	0.754349	0.129606	0.978652	115	166	108	381	338	283
rno-miR-223-5p	2.68372	0.008705	0.696377	5	3	0	21	38	23
rno-miR-224-5p	-0.78184	0.684397	0.978652	0	2	3	2	1	1
rno-miR-23a-3p	-0.67305	0.19527	0.978652	58	114	99	122	68	65
rno-miR-23b-3p	-0.91518	0.175486	0.978652	20	21	19	16	17	15
rno-miR-24-2-5p	0.248501	0.795821	0.978652	2	20	8	35	7	13
rno-miR-24-3p	0.371978	0.552507	0.978652	35	38	18	76	59	52
rno-miR-25-3p	0.513842	0.425343	0.978652	28	15	31	91	33	41
rno-miR-26a-5p	-0.29108	0.617169	0.978652	28	38	101	60	68	57
rno-miR-26b-3p	0.386058	0.924624	0.978652	0	0	0	0	0	1
rno-miR-26b-5p	0.605573	0.538772	0.978652	6	2	5	10	9	11
rno-miR-27a-3p	0.155975	0.77183	0.978652	113	209	104	265	255	203
rno-miR-27a-5p	1.945969	0.621438	0.978652	0	0	0	0	1	2

rno-miR-27b-3p	0.919674	0.08403	0.978652	261	858	795	1601	1373	2145
rno-miR-28-3p	-0.03385	0.962391	0.981664	7	18	15	21	16	20
rno-miR-28-5p	0.386058	0.924624	0.978652	0	0	0	0	0	1
rno-miR-299a-3p	-0.44106	0.796232	0.978652	6	0	4	12	0	1
rno-miR-299b-3p	0.386058	0.924624	0.978652	0	0	0	1	0	0
rno-miR-29a-3p	0.210462	0.654761	0.978652	125	238	288	324	365	376
rno-miR-29b-3p	-0.01704	0.977574	0.981664	66	217	80	234	141	174
rno-miR-29c-3p	0.819288	0.085716	0.978652	63	88	159	291	265	216
rno-miR-29c-5p	2.271213	0.528369	0.978652	0	0	0	2	2	0
rno-miR-300-3p	0.140307	0.971786	0.981664	0	1	0	2	0	0
rno-miR-301a-3p	0.601952	0.29307	0.978652	19	40	28	75	66	55
rno-miR-301a-5p	-2.49892	0.413865	0.978652	0	4	0	0	0	1
rno-miR-301b-3p	0.411366	0.725389	0.978652	0	15	4	17	15	5
rno-miR-3068-3p	0.801651	0.806275	0.978652	0	0	1	2	0	1
rno-miR-3068-5p	-1.4749	0.197079	0.978652	7	10	2	4	2	5
rno-miR-30a-3p	0.299918	0.708718	0.978652	3	37	33	45	53	25
rno-miR-30a-5p	0.056805	0.935248	0.978652	9	19	51	37	46	26
rno-miR-30b-3p	-0.57571	0.887799	0.978652	0	1	0	1	0	0
rno-miR-30b-5p	0.261766	0.67895	0.978652	12	30	58	47	62	52
rno-miR-30c-1-3p	-2.77179	0.344189	0.978652	4	0	0	1	0	0
rno-miR-30c-2-3p	-1.35467	0.691521	0.978652	0	1	1	1	0	0
rno-miR-30c-5p	0.45123	0.474356	0.978652	17	13	29	34	45	36
rno-miR-30d-3p	0.386058	0.924624	0.978652	0	0	0	1	0	0
rno-miR-30d-5p	-0.70724	0.371897	0.978652	11	22	84	22	50	18
rno-miR-30e-3p	-0.74924	0.279442	0.978652	13	17	44	16	18	26
rno-miR-30e-5p	0.412921	0.59945	0.978652	8	5	29	25	31	19

rno-miR-32-3p	1.10075	0.78607	0.978652	0	0	0	2	0	0
rno-miR-32-5p	2.635579	0.142073	0.978652	0	0	2	4	8	4
rno-miR-320-3p	-0.50941	0.818146	0.978652	0	2	4	0	5	0
rno-miR-322-5p	0.158792	0.77951	0.978652	24	64	50	104	66	58
rno-miR-324-3p	-1.62524	0.6099	0.978652	1	1	0	0	0	1
rno-miR-324-5p	-0.34881	0.696643	0.978652	3	17	13	18	5	15
rno-miR-326-3p	1.10075	0.78607	0.978652	0	0	0	2	0	0
rno-miR-328a-3p	-3.13602	0.352228	0.978652	2	0	1	0	0	0
rno-miR-33-5p	0.339041	0.756245	0.978652	3	8	8	11	1	23
rno-miR-331-3p	0.386058	0.924624	0.978652	0	0	0	0	0	1
rno-miR-335	0.386058	0.924624	0.978652	0	0	0	0	1	0
rno-miR-338-3p	0.386058	0.924624	0.978652	0	0	0	0	0	1
rno-miR-339-5p	-2.01746	0.14475	0.978652	8	3	4	2	0	4
rno-miR-340-3p	2.151175	0.565501	0.978652	0	0	0	3	0	1
rno-miR-340-5p	0.086683	0.950381	0.978933	0	1	11	7	5	4
rno-miR-342-3p	0.441543	0.862364	0.978652	0	0	3	1	0	4
rno-miR-345-3p	-0.75328	0.628741	0.978652	6	4	1	1	9	0
rno-miR-345-5p	-2.4606	0.542208	0.978652	0	2	0	0	0	0
rno-miR-3473	-0.07924	0.892705	0.978652	1340	555	709	1777	913	1361
rno-miR-34a-5p	-0.22566	0.736497	0.978652	40	46	21	65	24	59
rno-miR-34c-5p	0.386058	0.924624	0.978652	0	0	0	0	1	0
rno-miR-350	-1.13606	0.436142	0.978652	3	9	0	5	2	2
rno-miR-351-5p	1.912039	0.630498	0.978652	0	0	0	1	2	0
rno-miR-3559-5p	1.505075	0.597922	0.978652	0	1	0	4	0	1
rno-miR-3583-5p	0.386058	0.924624	0.978652	0	0	0	1	0	0
rno-miR-3586-3p	-1.21135	0.757428	0.978652	0	0	2	0	0	1

rno-miR-3590-3p	0.386058	0.924624	0.978652	0	0	0	0	1	0
rno-miR-361-3p	1.67694	0.675597	0.978652	0	0	0	3	0	0
rno-miR-361-5p	1.10075	0.78607	0.978652	0	0	0	2	0	0
rno-miR-362-5p	0.386058	0.924624	0.978652	0	0	0	1	0	0
rno-miR-365-3p	1.619872	0.510454	0.978652	1	0	0	2	1	2
rno-miR-369-3p	-1.18866	0.433064	0.978652	3	3	3	3	3	0
rno-miR-374-5p	-0.21384	0.937875	0.978652	0	0	3	0	1	2
rno-miR-378a-3p	0.42173	0.431089	0.978652	36	33	84	101	100	87
rno-miR-378a-5p	1.096245	0.612855	0.978652	2	0	0	6	1	1
rno-miR-378b	1.120232	0.119445	0.978652	8	6	15	26	25	39
rno-miR-379-5p	-0.4777	0.522276	0.978652	53	14	22	43	23	40
rno-miR-382-5p	-2.93153	0.067584	0.978652	7	3	5	0	0	3
rno-miR-409a-5p	-2.73444	0.495841	0.978652	2	0	0	0	0	0
rno-miR-411-5p	-0.44631	0.888033	0.978652	0	0	3	3	0	0
rno-miR-421-3p	-1.5375	0.706327	0.978652	0	0	1	0	0	0
rno-miR-423-3p	0.386058	0.924624	0.978652	0	0	0	1	0	0
rno-miR-423-5p	0.554454	0.720929	0.978652	1	0	6	7	1	6
rno-miR-425-5p	0.537108	0.850262	0.978652	0	0	2	3	0	1
rno-miR-448-3p	2.379665	0.497463	0.978652	0	0	0	0	2	2
rno-miR-449a-5p	-0.57571	0.887799	0.978652	0	1	0	0	0	1
rno-miR-450a-3p	-2.73444	0.495841	0.978652	2	0	0	0	0	0
rno-miR-451-5p	0.259888	0.831839	0.978652	5	0	9	11	10	3
rno-miR-452-5p	-1.49827	0.58067	0.978652	3	0	0	1	0	1
rno-miR-455-5p	1.757621	0.660514	0.978652	0	0	0	2	0	1
rno-miR-466b-5p	1.990768	0.295576	0.978652	0	2	0	5	5	2
rno-miR-466c-5p	-3.95197	0.036114	0.978652	3	5	3	1	0	0

rno-miR-483-5p	-2.73444	0.495841	0.978652	2	0	0	0	0	0
rno-miR-486	-0.90245	0.759819	0.978652	2	0	0	1	0	1
rno-miR-487b-3p	-0.57571	0.887799	0.978652	0	0	1	1	0	0
rno-miR-488-3p	1.67694	0.675597	0.978652	0	0	0	3	0	0
rno-miR-490-3p	-1.5375	0.706327	0.978652	0	0	1	0	0	0
rno-miR-494-3p	-0.78035	0.65485	0.978652	5	0	3	6	0	2
rno-miR-495	0.138977	0.972663	0.981664	0	0	1	2	0	0
rno-miR-497-5p	-1.5375	0.706327	0.978652	1	0	0	0	0	0
rno-miR-499-5p	-1.97233	0.506236	0.978652	1	0	2	0	1	0
rno-miR-500-3p	0.386058	0.924624	0.978652	0	0	0	1	0	0
rno-miR-503-5p	-1.39614	0.063739	0.978652	13	13	23	9	7	11
rno-miR-505-5p	-0.57571	0.887799	0.978652	0	1	0	0	0	1
rno-miR-511-3p	-2.17089	0.592683	0.978652	0	0	2	0	0	0
rno-miR-532-5p	1.71455	0.003716	0.445886	18	59	28	189	168	155
rno-miR-542-3p	-0.84458	0.63772	0.978652	0	1	10	6	2	0
rno-miR-542-5p	0.142509	0.942238	0.978933	2	0	2	4	0	3
rno-miR-582-5p	-0.57571	0.887799	0.978652	1	0	0	0	1	0
rno-miR-598-3p	-3.75501	0.20061	0.978652	0	1	5	0	0	0
rno-miR-632	0.386058	0.924624	0.978652	0	0	0	1	0	0
rno-miR-6333	0.386058	0.924624	0.978652	0	0	0	1	0	0
rno-miR-652-3p	0.37094	0.872442	0.978652	1	0	3	8	0	0
rno-miR-664-2-5p	0.386058	0.924624	0.978652	0	0	0	1	0	0
rno-miR-674-3p	0.461532	0.899831	0.978652	1	0	0	0	2	0
rno-miR-674-5p	-0.45599	0.615142	0.978652	11	5	9	16	5	8
rno-miR-702-5p	0.386058	0.924624	0.978652	0	0	0	1	0	0
rno-miR-708-5p	-1.5375	0.706327	0.978652	1	0	0	0	0	0

rno-miR-770-5p	0.386058	0.924624	0.978652	0	0	0	0	0	1
rno-miR-7a-5p	-1.02837	0.125223	0.978652	13	50	34	25	19	25
rno-miR-872-3p	-0.60275	0.697298	0.978652	3	2	3	2	0	6
rno-miR-872-5p	-0.36489	0.753922	0.978652	3	5	3	5	3	5
rno-miR-92a-3p	0.29952	0.918627	0.978652	2	0	0	0	4	0
rno-miR-93-5p	0.352456	0.510203	0.978652	59	39	89	170	97	90
rno-miR-98-5p	-0.41966	0.744361	0.978652	6	3	1	3	6	3
rno-miR-99a-5p	0.483218	0.6464	0.978652	1	3	14	9	15	8
rno-miR-99b-5p	-0.57985	0.646455	0.978652	0	3	33	7	17	4
rno-miR-9a-5p	0.113466	0.965747	0.981664	0	0	3	1	0	3

Table S8: Protein profiling results of EV-free IL-4-MΦ-CM

Accession	Gene	Description
P63259	Actg1	Actin, cytoplasmic 2
P62329	Tmsb4x	Thymosin beta-4
Q6IN37	Gm2a	GM2 ganglioside activator
Q6P6T6	Ctsd	Cathepsin D
Q6P7C7	Gpnmb	Transmembrane glycoprotein NMB
Q5XFV4	Fabp4	Fabp4 protein
P05942	S100a4	Protein S100-A4
P62963	Pfn1	Profilin-1
P06302	Ptma	Prothymosin alpha
P05964	S100a6	Protein S100-A6
F1M8E9	Lyz2	Lysozyme
Q6IN22	Ctsb	Cathepsin B
P04797	Gapdh	Glyceraldehyde-3-phosphate dehydrogenase
B0BNA5	Cotl1	Coactosin-like protein
Q07936	Anxa2	Annexin A2
F7FJQ3	Npc2	NPC intracellular cholesterol transporter 2
A0A0G2JXB1	Lgals3	Galectin
P11762	Lgals1	Galectin-1
G3V8C3	Vim	Vimentin
P11232	Txn	Thioredoxin

P05065	Aldoa	Fructose-bisphosphate aldolase A
P62260	Ywhae	14-3-3 protein epsilon
P02650	Apoe	Apolipoprotein E
Q6AYC4	Capg	Macrophage-capping protein
Q5XI73	Arhgdia	Rho GDP-dissociation inhibitor 1
P85973	Pnp	Purine nucleoside phosphorylase
Q00715		Histone H2B type 1
P69897	Tubb5	Tubulin beta-5 chain
P04642	Ldha	L-lactate dehydrogenase A chain
P62986	Uba52	Ubiquitin-60S ribosomal protein L40
P0DP31	Calm3	Calmodulin-3
P09495	Tpm4	Tropomyosin alpha-4 chain
P07335	Ckb	Creatine kinase B-type
Q5XI38	Lcp1	Lymphocyte cytosolic protein 1
P63102	Ywhaz	14-3-3 protein zeta/delta
Q9EPB1	Dpp7	Dipeptidyl peptidase 2
A0A0G2K3Z9		Uncharacterized protein
P48500	Tpi1	Triosephosphate isomerase
P07151	B2m	Beta-2-microglobulin
P50137	Tkt	Transketolase
Q9R1T3	Ctsz	Cathepsin Z
P45592	Cfl1	Cofilin-1

Q62658	Fkbp1a	Peptidyl-prolyl cis-trans isomerase FKBP1A
P14841	Cst3	Cystatin-C
P14668	Anxa5	Annexin A5
B2RZ27	Sh3bgrl3	SH3 domain binding glutamic acid-rich protein-like 3
A0A0G2JSS8	Prdx5	Peroxiredoxin
P63312	Tmsb10	Thymosin beta-10
A0A0H2UHM7	LOC100909441	Tubulin alpha chain
P19804	Nme2	Nucleoside diphosphate kinase B
A0A0G2K1C0	Actr3	Actin-related protein 3
P11030	Dbi	Acyl-CoA-binding protein
P08721	Spp1	Osteopontin
D3ZSL2	Abrac1	ABRA C-terminal-like
P19944	Rplp1	60S acidic ribosomal protein P1
Q6B345	S100a11	Protein S100-A11
P01041	Cstb	Cystatin-B
A0A0G2JVG3	Pkm	Pyruvate kinase
D4A4S3	Hspa8	Heat shock cognate 71 kDa protein
P55053	Fabp5	Fatty acid-binding protein 5
Q5U362	Anxa4	Annexin
P07150	Anxa1	Annexin A1
P63029	Tpt1	Translationally-controlled tumor protein
M0R5J4		Uncharacterized protein

D3ZZR3	Ctss	Cathepsin S
P82995	Hsp90aa1	Heat shock protein HSP 90-alpha
R9PXT7	Mmp12	Macrophage metalloelastase
P10111	Ppia	Peptidyl-prolyl cis-trans isomerase A
A0A0G2JWE1	Myl6	Myosin light polypeptide 6
A0A0G2JSH9	Prdx2	Peroxiredoxin-2
P80067	Ctsc	Dipeptidyl peptidase 1
P07154	Ctsl	Cathepsin L1
P25113	Pgam1	Phosphoglycerate mutase 1
P04636	Mdh2	Malate dehydrogenase, mitochondrial
M0R757	LOC100360413	Elongation factor 1-alpha
P50399	Gdi2	Rab GDP dissociation inhibitor beta
P04906	Gstp1	Glutathione S-transferase P
P31044	Pebp1	Phosphatidylethanolamine-binding protein 1
A0A1W2Q6E9	Msn	Moesin
Q06000	Lpl	Lipoprotein lipase
Q5EBB0	LOC298795	Similar to 14-3-3 protein sigma
Q920A6	Scpep1	Retinoid-inducible serine carboxypeptidase
Q641Z7	Smpdl3a	Acid sphingomyelinase-like phosphodiesterase 3a
Q5XFX0	Tagln2	Transgelin-2
Q8VHC1	Cst6	Cystatin E/M
P34058	Hsp90ab1	Heat shock protein HSP 90-beta

Q66H12	Naga	Alpha-N-acetylgalactosaminidase
P85968	Pgd	6-phosphogluconate dehydrogenase, decarboxylating
A0A0G2JSV6	Hba-a2	Globin c2
D4ACV3	Hist2h2ac	Histone H2A
Q5M860	Arhgdib	Rho GDP dissociation inhibitor beta
D3ZJ08	Hist2h3c2	Histone H3
Q6Q0N1	Cndp2	Cytosolic non-specific dipeptidase
Q5PPG2	Lgmn	Legumain
Q63610	Tpm3	Tropomyosin alpha-3 chain
Q9WUC4	Atox1	Copper transport protein ATOX1
O88656	Arpc1b	Actin-related protein 2/3 complex subunit 1B
P51635	Akr1a1	Aldo-keto reductase family 1 member A1
Q9EQS0	Taldo1	Transaldolase
Q3T1J1	Eif5a	Eukaryotic translation initiation factor 5A-1
Q6P6V0	Gpi	Glucose-6-phosphate isomerase
A0A0G2JSU3	Set	Protein SET
P05197	Eef2	Elongation factor 2
Q6AYS3	Ctsa	Carboxypeptidase
G3V786	Akr1b8	Aldo-keto reductase family 1, member B8
P62775	Mtpn	Myotrophin
P35467	S100a1	Protein S100-A1
Q5U2V4	Plbd1	Phospholipase B-like 1

F1M2K3	Sumo2	Small ubiquitin-related modifier
D4A4D5	LOC498555	Similar to 60S acidic ribosomal protein P2
P61983	Ywhag	14-3-3 protein gamma
P18418	Calr	Calreticulin
Q62714	Np4	Neutrophil antibiotic peptide NP-4
Q3MIE4	Vat1	Synaptic vesicle membrane protein VAT-1 homolog
F1LMW7	Marcks	Myristoylated alanine-rich C-kinase substrate
Q6IMZ3	Anxa6	Annexin
Q499T2	Ifi30	Gamma-interferon-inducible lysosomal thiol reductase
Q6AXR4	Hexb	Beta-hexosaminidase subunit beta
Q5M7U6	Actr2	Actin-related protein 2
B2GV73	Arpc3	Actin-related protein 2/3 complex subunit 3
P04785	P4hb	Protein disulfide-isomerase
D3ZE63		Uncharacterized protein
A0A0G2K4H6	Galns	N-acetylgalactosamine-6-sulfatase
A0A0G2K9A2	Arpc2	Arp2/3 complex 34 kDa subunit
Q6MG61	Clic1	Chloride intracellular channel protein 1
D4A954	LOC100360143	Similar to Spleen protein 1 precursor (RSP-1)
Q9Z0V5	Prdx4	Peroxiredoxin-4
P35213	Ywhab	14-3-3 protein beta/alpha
A0A0G2K013	Actn4	Alpha-actinin-4
P10960	Psap	Prosaposin

D3ZH55	Fam53c	Family with sequence similarity 53, member C
P07895	Sod2	Superoxide dismutase [Mn], mitochondrial
Q5RKI0	Wdr1	WD repeat-containing protein 1
P50430	Arsb	Arylsulfatase B
D4A6R4	LOC100362216	Hypothetical protein LOC100362216
P06760	Gusb	Beta-glucuronidase
Q68FP1	Gsn	Gelsolin
E9PSP1	Pltp	Phospholipid transfer protein
Q08163	Cap1	Adenylyl cyclase-associated protein 1
P85971	Pgls	6-phosphogluconolactonase
P05370	G6pdx	Glucose-6-phosphate 1-dehydrogenase
P27926	Hk3	Hexokinase-3
P62804	Hist1h4b	Histone H4
B5DF65	Blvrb	Biliverdin reductase B
P46462	Vcp	Transitional endoplasmic reticulum ATPase
P16617	Pgk1	Phosphoglycerate kinase 1
Q6P7Q4	Glo1	Lactoylglutathione lyase
Q3T1K5	Capza2	F-actin-capping protein subunit alpha-2
Q6P9V7	Psme1	Proteasome (Prosome, macropain) activator subunit 1
Q5M7T7	Pla2g7	Platelet-activating factor acetylhydrolase
Q91ZN1	Coro1a	Coronin-1A
O88989	Mdh1	Malate dehydrogenase, cytoplasmic

A0A0G2JUD9	Mmp9	Matrix metalloproteinase-9
Q4KLZ0	Vnn1	Vanin 1
D3ZUM4	Glb1	Beta-galactosidase
D3ZD31	Mrc1	Mannose receptor, C type 1
P47942	Dpysl2	Dihydropyrimidinase-related protein 2
F1LRC2	Aif1	Allograft inflammatory factor 1
F1M779	Cltc	Clathrin heavy chain
G3V7C6	Tubb4b	Tubulin beta chain
O70509	Cd44	CD44 antigen
G3V6D3	Atp5f1b	ATP synthase subunit beta
Q63798	Psme2	Proteasome activator complex subunit 2
F1M8F4	Gmfg	Glia maturation factor
B2RZ72	Arpc4	Actin-related protein 2/3 complex subunit 4
Q6P686	Ostf1	Osteoclast-stimulating factor 1
Q9EQX9	Ube2n	Ubiquitin-conjugating enzyme E2 N
P13084	Npm1	Nucleophosmin
P68511	Ywhah	14-3-3 protein eta
Q8CFN2	Cdc42	Cell division control protein 42 homolog
P68255	Ywhaq	14-3-3 protein theta
P13221	Got1	Aspartate aminotransferase, cytoplasmic
F1M5C9	Ube2d2	Ubiquitin-conjugating enzyme E2 D2
Q4KMA2	Rad23b	UV excision repair protein RAD23 homolog B

P22734	Comt	Catechol O-methyltransferase
P06762	Hmox1	Heme oxygenase 1
D4A8F2	Rsu1	Ras suppressor protein 1
P11598	Pdia3	Protein disulfide-isomerase A3
Q9JKB7	Gda	Guanine deaminase
D4A133	Atp6v1a	ATPase H ⁺ -transporting V1 subunit A
P17046	Lamp2	Lysosome-associated membrane glycoprotein 2
Q6P7S1	Asah1	Acid ceramidase
Q6P9V9	Tuba1b	Tubulin alpha-1B chain
P01346	Igf2	Insulin-like growth factor II
P62828	Ran	GTP-binding nuclear protein Ran
Q5I0D7	Pepd	Xaa-Pro dipeptidase
F1M978	Impa1	Inositol-1-monophosphatase
P05982	Nqo1	NAD(P)H dehydrogenase [quinone] 1
P10760	Ahcy	Adenosylhomocysteinase
B5DEN5	Eef1b2	Eukaryotic translation elongation factor 1 beta 2
P60901	Psma6	Proteasome subunit alpha type-6
P54313	Gnb2	Guanine nucleotide-binding protein G(I)/G(S)/G(T) subunit beta-2
O88767	Park7	Protein/nucleic acid deglycase DJ-1
B2RYQ5	Erh	Enhancer of rudimentary homolog
C0JPT7	Flna	Filamin A

G3V7Q7	Iqgap1	IQ motif containing GTPase activating protein 1 (Predicted), isoform CRA_b
A0A0G2JSG6	Ak2	Adenylate kinase 2, mitochondrial
E2RUH2	Rnh1	Ribonuclease inhibitor
Q6JE36	Ndrp1	Protein NDRG1
A0A0G2JUB0	Fam3c	Protein FAM3C
P12346	Tf	Serotransferrin
F1LQS6	Xdh	RCG61833
P07632	Sod1	Superoxide dismutase [Cu-Zn]
Q6MG73	C2	Complement C2
D4A2F6	Nhlrc3	NHL repeat-containing 3
D4AA31	Prcp	Prolylcarboxypeptidase
D4A2G9	Ranbp1	RAN-binding protein 1
O35244	Prdx6	Peroxiredoxin-6
P40112	Psmb3	Proteasome subunit beta type-3
A0A0G2JSW0	My12b	Myosin regulatory light chain 12B
G3V852	Tln1	RCG55135, isoform CRA_b
M0RDJ4	Gmfb	Glia maturation factor
P52555	Erp29	Endoplasmic reticulum resident protein 29
Q5M7T5	Serpinc1	Serine (Or cysteine) peptidase inhibitor, clade C (Antithrombin), member 1
G3V8L3	Lmna	Lamin A, isoform CRA_b

F1LM82	Hnrnpa2b1	Heterogeneous nuclear ribonucleoproteins A2/B1
P40307	Psmb2	Proteasome subunit beta type-2
P06761	Hspa5	Endoplasmic reticulum chaperone BiP
R9PXU6	Vcl	Vinculin
Q641X3	Hexa	Beta-hexosaminidase subunit alpha
G3V904	Plid4	Phospholipase D family, member 4
D3ZAT4	Serpina9	Serine (Or cysteine) peptidase inhibitor, clade A (Alpha-1 antiproteinase, antitrypsin), member 9 (Predicted)
P07943	Akr1b1	Aldo-keto reductase family 1 member B1
Q6P3V8	Eif4a1	Eukaryotic translation initiation factor 4A1
P45479	Ppt1	Palmitoyl-protein thioesterase 1
A0A0G2K5R9	RGD1560860	Similar to ankyrin repeat domain 26
Q4QQV6	Lsp1	Lymphocyte specific 1, isoform CRA_a
P04916	Rbp4	Retinol-binding protein 4
Q499P2	Lta4h	Leukotriene A(4) hydrolase
P30121	Timp2	Metalloproteinase inhibitor 2
A0A0G2K1E1	RT1-A1	RT1 class Ia, locus A1
F1LP34	Anp32b	Acidic leucine-rich nuclear phosphoprotein 32 family member B
P62815	Atp6v1b2	V-type proton ATPase subunit B, brain isoform
Q68FR6	Eef1g	Elongation factor 1-gamma
G3V6E7	Fmod	Fibromodulin

P36972	Aprt	Adenine phosphoribosyltransferase
B0BMY7	Twf2	Protein tyrosine kinase 9-like (A6-related protein) (Predicted), isoform CRA_b
P19945	Rplp0	60S acidic ribosomal protein P0
F1MAB9	Tpd52	Tumor protein D52
P38983	Rpsa	40S ribosomal protein SA
B5DFD8	Sh3bgrl	SH3 domain-binding glutamic acid-rich-like protein
Q9Z2G8	Nap1l1	Nucleosome assembly protein 1-like 1
D3ZB30	Ptbp1	Polypyrimidine tract binding protein 1, isoform CRA_c
Q675A5	Pla2g15	Group XV phospholipase A2
Q5XI32	Capzb	F-actin-capping protein subunit beta
P27139	Ca2	Carbonic anhydrase 2
G3V940	Coro1b	Coronin
Q62669	LOC103694855	Beta-globin
D3ZZ89	Trem2	Triggering receptor expressed on myeloid cells 2 (Predicted), isoform CRA_a
A0A0H2UHL6	Ctsh	Pro-cathepsin H
G3V6P7	Myh9	Myosin heavy chain 9-like 1
G3V7H3	Cfd	Complement factor D
F1LVC3	Rab6b	RAB6B, member RAS oncogene family
Q5U300	Uba1	Ubiquitin-like modifier-activating enzyme 1
O35567	Atic	Bifunctional purine biosynthesis protein PURH

D3ZF11	Lamtor5	Hepatitis B virus x interacting protein (Predicted), isoform CRA_a
A0A0G2JYS8	Ppp1ca	Serine/threonine-protein phosphatase
G3V8C4	Clic4	Chloride intracellular channel protein
M0RCH5	Gnpda1	Glucosamine-6-phosphate isomerase
P62994	Grb2	Growth factor receptor-bound protein 2
P83868	Ptges3	Prostaglandin E synthase 3
G3V826	Tkt	Transketolase
P00507	Got2	Aspartate aminotransferase, mitochondrial
B2GVB9	Fermt3	Fermitin family member 3
P17220	Psma2	Proteasome subunit alpha type-2
A0A0G2JXT0	Vps26a	Vacuolar protein sorting-associated protein 26A
P50398	Gdi1	Rab GDP dissociation inhibitor alpha
Q62667	Mvp	Major vault protein
A0A0G2K2V2	Ap1b1	AP complex subunit beta
Q62636	Rap1b	Ras-related protein Rap-1b
F1LMP7	Grn	Progranulin
Q5XIF6	Tuba4a	Tubulin alpha-4A chain
Q66HH8	Anxa5	Annexin
Q66HD0	Hsp90b1	Endoplasmin
M0RCS3		Ferritin
Q63081	Pdia6	Protein disulfide-isomerase A6

P61980	Hnrnpk	Heterogeneous nuclear ribonucleoprotein K
A0A0G2K4Q4		Uncharacterized protein
O35828	Coro7	Coronin-7
O89049	Txnrd1	Thioredoxin reductase 1, cytoplasmic
Q6GMN8	Actn1	Actn1 protein
A0A0H2UHE2	Il1rn	Interleukin-1
P21670	Psma4	Proteasome subunit alpha type-4
Q68FS4	Lap3	Cytosol aminopeptidase
O70513	Lgals3bp	Galectin-3-binding protein
P13668	Stmn1	Stathmin
G3V9Q3	Hnrnph1	Heterogeneous nuclear ribonucleoprotein H
Q63041	A1m	Alpha-1-macroglobulin
Q5XI34	Ppp2r1a	Protein phosphatase 2 (Formerly 2A), regulatory subunit A (PR 65), alpha isoform, isoform CRA_a
D3ZVB7	Ogn	Osteoglycin
Q5XIM9	Cct2	T-complex protein 1 subunit beta
Q4KM35	Psmb10	Proteasome subunit beta type-10
P63245	Rack1	Receptor of activated protein C kinase 1
D3ZUL3	Col6a1	Collagen type VI alpha 1 chain
Q7TPB1	Cct4	T-complex protein 1 subunit delta
Q4KM75	Cd5l	CD5 antigen-like
F7EQ81	Gns	N-acetylglucosamine-6-sulfatase

B0BNN4	Cfp	Complement factor properdin
D4A8G5	Tgfb1	Transforming growth factor, beta-induced
B0K010	Txndc17	Thioredoxin domain-containing 17
F1M7X3	Cdh13	Cadherin 13
Q5XIE0	Anp32e	Acidic leucine-rich nuclear phosphoprotein 32 family member E
B2GUZ5	Capza1	F-actin-capping protein subunit alpha-1
P85515	Actr1a	Alpha-centractin
D4AC23	Cct7	T-complex protein 1 subunit eta
F1LMS5	Thbs4	Thrombospondin-4
A0A0G2K943	Ap2a2	AP-2 complex subunit alpha
Q91Y81	Sept2	Septin-2
B2GUX7	Creg1	Cellular repressor of E1A-stimulated genes (Predicted), isoform CRA_b
B2RYG6	Otub1	Ubiquitin thioesterase OTUB1
P02454	Col1a1	Collagen alpha-1(I) chain
F1LST1	Fn1	Fibronectin
B0BNJ1	Sri	LOC683667 protein
P09606	Glul	Glutamine synthetase
Q5I0D1	Glod4	Glyoxalase domain-containing protein 4
Q9QX80	Hnrnpab	CARG-binding factor A
A0A0G2K911	Nsf1c	NSFL1 cofactor p47

Q9JLJ3	Aldh9a1	4-trimethylaminobutyraldehyde dehydrogenase
R9PXS4	Pitpna	Phosphatidylinositol transfer protein alpha isoform
F1LRV4	Hspa4	Heat shock 70 kDa protein 4
P16296	F9	Coagulation factor IX
P14562	Lamp1	Lysosome-associated membrane glycoprotein 1
Q71SY3	Tsn	Translin
Q66WT9	Picalm	Clathrin-assembly lymphoid myeloid leukemia protein
D3ZZL3	Naglu	N-acetyl-alpha-glucosaminidase
F1M6Z1	Apob	Apolipoprotein B-100
P70645	Blmh	Bleomycin hydrolase
Q7M0E3	Dstn	Destrin
P11980	Pkm	Pyruvate kinase PKM
D4AEH3	Psmc7	Proteasome (Prosome, macropain) 26S subunit, non-ATPase, 7 (Predicted)
A0A096MJ04	Gsto1	Glutathione S-transferase omega 1, isoform CRA_a
F1M9V7	Npepps	Aminopeptidase
A0A0G2KAT4	Ddx39b	Spliceosome RNA helicase Ddx39b
B2RYC9	Gba	Glucosylceramidase
O70257	Stx7	Syntaxin-7
O55096	Dpp3	Dipeptidyl peptidase 3
A0A0G2K0W9	Psma7	Proteasome subunit alpha type
Q4KM73	Cmpk1	UMP-CMP kinase

M0R544	Gaa	Glucosidase, alpha, acid, isoform CRA_a
Q68FR9	Eef1d	Elongation factor 1-delta
F1M9B9	Il1rap	Interleukin-1 receptor accessory protein
Q6P502	Cct3	T-complex protein 1 subunit gamma
G3V8A5	Vps35	Vacuolar protein sorting-associated protein 35
Q641Z6	Ehd1	EH domain-containing protein 1
Q07009	Capn2	Calpain-2 catalytic subunit
A0A0G2K890	Ezr	Ezrin
D3ZVH2		Uncharacterized protein
P29066	Arrb1	Beta-arrestin-1
Q5FVI6	Atp6v1c1	V-type proton ATPase subunit C 1
M0RB74	Ipo5	Importin 5
Q7TQ94	Nit1	Deaminated glutathione amidase
P52296	Kpnb1	Importin subunit beta-1
B0BN93	Psmd13	26S proteasome non-ATPase regulatory subunit 13
Q711G3	Iah1	Isoamyl acetate-hydrolyzing esterase 1 homolog
P97536	Cand1	Cullin-associated NEDD8-dissociated protein 1
Q68FR2	Bin2	Bridging integrator 2
D3ZV60	Cenpe	Centromere protein E
Q5XIM7	Kars	Lysine--tRNA ligase
Q7TQ70	Fga	Ac1873
F1M7X5	Dpp4	Dipeptidyl peptidase 4

Q3MHS9	Cct6a	Chaperonin containing Tcp1, subunit 6A (Zeta 1)
Q68FQ0	Cct5	T-complex protein 1 subunit epsilon
P41562	Idh1	Isocitrate dehydrogenase [NADP] cytoplasmic
G3V6T7	Pdia4	Protein disulfide-isomerase A4
F1LMZ8	Psmd11	26S proteasome non-ATPase regulatory subunit 11
M0RD54	CEFIP	Cardiac-enriched FHL2-interacting protein
A0A0G2JSK9	Bhmt	Betaine--homocysteine S-methyltransferase 1
Q4G075	Serpib1a	Leukocyte elastase inhibitor A
D3ZVQ0	Usp5	Ubiquitin carboxyl-terminal hydrolase
Q68FX4	Hcls1	Hematopoietic cell-specific LYN substrate 1
Q9ESQ7	Psd	PH and SEC7 domain-containing protein 1
F7EPH4	Ppa1	Pyrophosphatase (inorganic) 1
A0A0G2K5E8	NEWGENE_621351	Collagen, type I, alpha 2
A0A0G2K509	Krt5	Keratin, type II cytoskeletal 5
Q5XI58	Ccin	Calicin
P04961	Pcna	Proliferating cell nuclear antigen
P14408	Fh	Fumarate hydratase, mitochondrial
D3ZL24	Cast	Calpastatin
A0A0A0MY22	Siae	Sialate O-acetyltransferase
G3V6S2	Aco1	Cytoplasmic aconitate hydratase
G3V824	Igf2r	Insulin-like growth factor 2 receptor
Q63768	Crk	Adapter molecule crk

P46413	Gss	Glutathione synthetase
A0A0G2JU96	Ahnak	AHNAK nucleoprotein
D3ZDT1	Epb41l2	Erythrocyte membrane protein band 4.1-like 2
Q4FZY0	Efhd2	EF-hand domain-containing protein D2
Q8R3Z7	Ehd4	EH-domain-containing 4
A0A0G2K666	Kcnq4	Potassium voltage-gated channel subfamily KQT member 4
Q6P762	Man2b1	Alpha-mannosidase
Q6AXW2	Tmod3	RCG25684, isoform CRA_a
Q4FZV0	Manba	Beta-mannosidase
Q9Z1X1	Esyt1	Extended synaptotagmin-1
D4ACB8	Cct8	Chaperonin subunit 8 (Theta) (Predicted), isoform CRA_a
D3ZE62	Atp8b3	Phospholipid-transporting ATPase
Q01460	Ctbs	Di-N-acetylchitobiase
P53534	Pygb	Glycogen phosphorylase, brain form (Fragment)
Q4AEF8	Copg1	Coatomer subunit gamma-1
G3V928	Lrp1	LDL receptor-related protein 1
O35763	Msn	Moesin
Q03336	Rgn	Regucalcin
Q63083	Nucb1	Nucleobindin-1
A0A0G2JYA4	LOC100362453	Serine/threonine-protein phosphatase

A0A0G2K1J5	Plec	Plectin
A0A0G2K2W1		Uncharacterized protein
A0A0G2K7R7	Rnf216	Ring finger protein 216
A0A0G2K9E8	Myo1e	Unconventional myosin-Ie
D3ZBN0	Hist1h1b	Histone H1.5
F1LZ64	Abhd12b	Abhydrolase domain-containing 12B
M0R4B6	LOC102555453	RCG64424
M0RAM5	Gpx1	Glutathione peroxidase
P28480	Tcp1	T-complex protein 1 subunit alpha
P41542	Uso1	General vesicular transport factor p115
P50503	St13	Hsc70-interacting protein
Q5U2S5	Snx24	Sorting nexin-24
Q6AXN2	Efemp1	EGF-containing fibulin-like extracellular matrix protein 1
Q6IMY6	Lipa	Lipase
Q6IUU3	Qsox1	Sulfhydryl oxidase 1
Q6PDW1	Rps12	40S ribosomal protein S12
Q6PDW4	Psmb1	Proteasome subunit beta
A0A096MJJ6	Acbd5	Acyl-CoA-binding domain-containing protein 5
A0A0G2JVH1	Myo5b	Unconventional myosin-Vb
A0A0G2K2T4	Lrp4	Low-density lipoprotein receptor-related protein 4
A0A0G2K7N8	Bptf	Uncharacterized protein
A0A0G2K8L5		Uncharacterized protein

A0A0G2KAG3	Atp6v1g2	ATPase H ⁺ -transporting V1 subunit G2
B1WC92	RGD1561552	RGD1561552 protein
B5DFK6	Ap3d1	Adaptor-related protein complex 3 subunit delta 1
D3Z851	Fbxl21	F-box and leucine-rich repeat protein 21
D3ZE01	Kif14	Kinesin family member 14
D3ZE91	Kctd9	Potassium channel tetramerisation domain containing 9 (Predicted), isoform CRA_b
D3ZFJ0	Pik3cg	Phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit gamma
D3ZGB8	Cilp	Cartilage intermediate layer protein
D3ZKH2	Mon2	MON2 homolog, regulator of endosome-to-Golgi- trafficking
D3ZQE8	Xpo5	Exportin 5
D3ZQI6	Xpo4	Exportin 4
D3ZY40	Pcf11	PCF11 cleavage and polyadenylation factor subunit
D3ZYB8	Tex15	Testis-expressed 15, meiosis and synapsis-associated
D4A1D3	Sacs	Sacsin molecular chaperone
D4A4D3	Tet1	Tet methylcytosine dioxygenase 1
D4A5Q2	Smc2	Structural maintenance of chromosomes protein
D4A5S1	Usp26	RCG53229
D4A624	Sgo1	Shugoshin 1
F1LVL5	Shroom4	Shroom family member 4

F1LY25	Kcnq5	Potassium voltage-gated channel subfamily Q member 5
F1M775	Diaph1	Protein diaphanous homolog 1
F1M974	Nsmaf	Neutral sphingomyelinase activation-associated factor
F7FKK4	Atxn7l2	Ataxin 7-like 2
G3V8K3	LOC100911109	Sperm associated antigen 4, isoform CRA_b
M0R9N9	Mbtd1	Mbt domain-containing 1
M0RCI4		Uncharacterized protein
P18266	Gsk3b	Glycogen synthase kinase-3 beta
P60711	Actb	Actin, cytoplasmic 1
P63041	Cplx1	Complexin-1
P68136	Acta1	Actin, alpha skeletal muscle
Q2HWF0	Fnbp1l	Formin-binding protein 1-like
Q3T1I3	Ushbp1	Usher syndrome type-1C protein-binding protein 1
Q5I0J2	Mad2l1bp	MAD2L1-binding protein
Q5PQK4	Uimc1	BRCA1-A complex subunit RAP80
Q63358	Myo9b	Unconventional myosin-Ixb
Q64595	Prkg2	cGMP-dependent protein kinase 2
Q68FU8	Sugp1	SURP and G-patch domain-containing protein 1
Q6AXT3	Arl13a	ADP-ribosylation factor-like protein 13A
Q6IMY8	Hnrnpu	Heterogeneous nuclear ribonucleoprotein U
Q6P5P3	Ttc9c	Tetratricopeptide repeat protein 9C

Q78E60	Arnt2	Aryl hydrocarbon receptor nuclear translocator 2
Q8VIP2	Mlxip1	Carbohydrate-responsive element-binding protein

Supplementary Figures

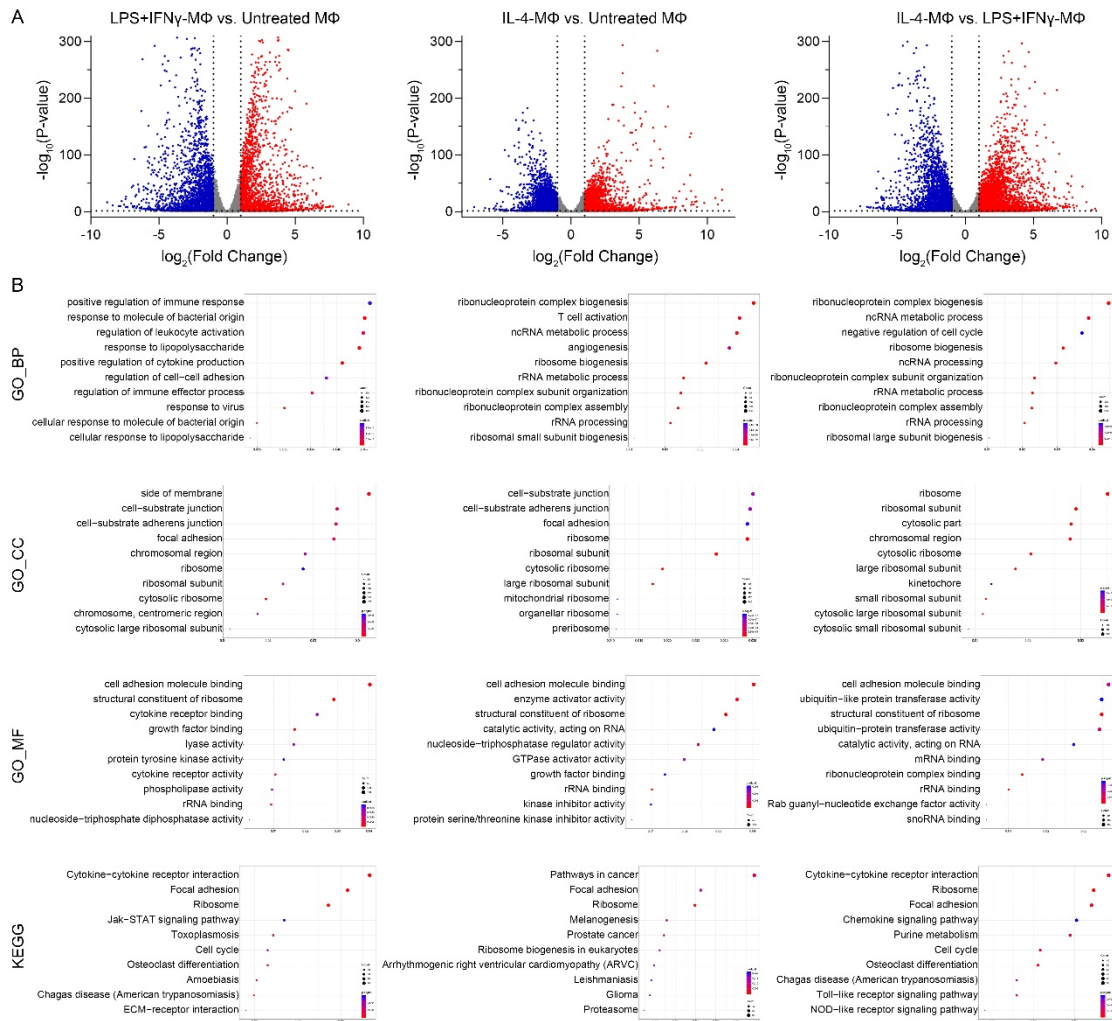


Figure S1: RNA-seq analysis of rat BMDMs

(A) Volcano Plot of RNA-seq of rat BMDMs. Red dots represent upregulated genes; blue dots represent downregulated genes. (B) GO and KEGG Enrichment analysis of RNA-seq of rat BMDMs.

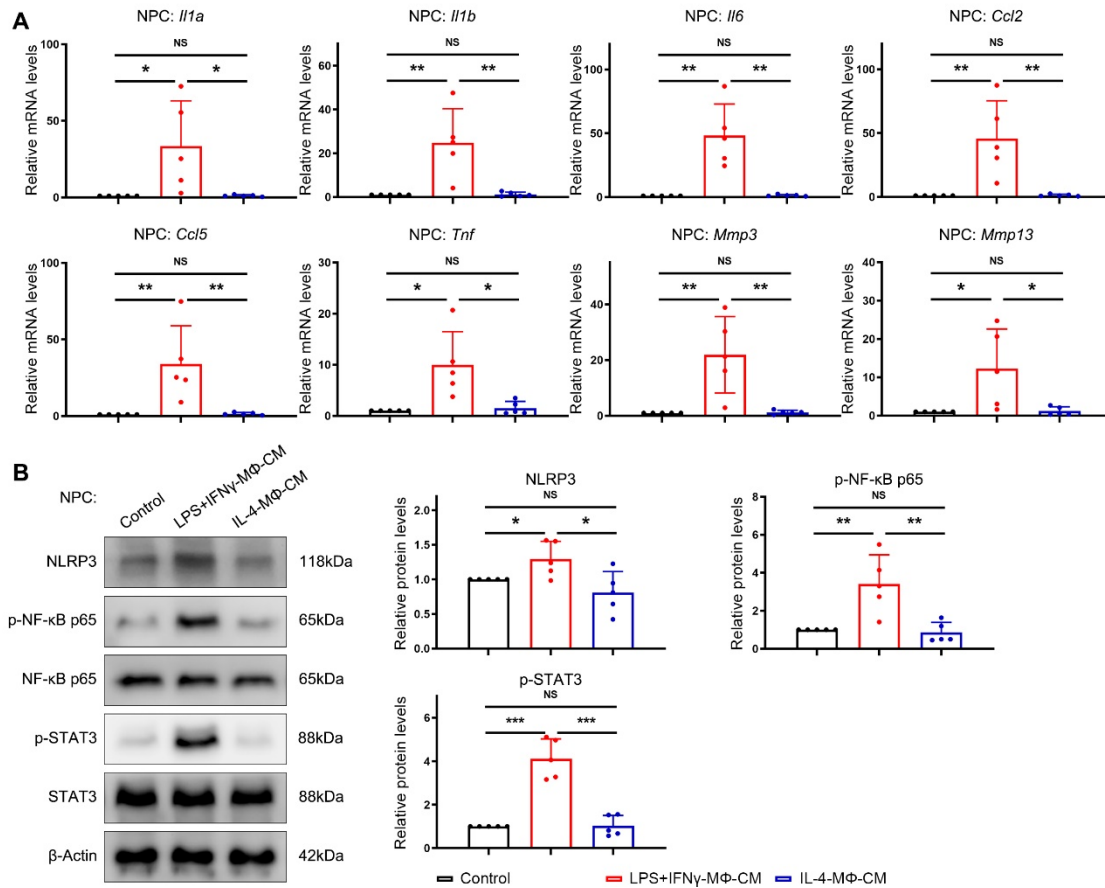


Figure S2: LPS+IFN γ -M Φ -CM stimulated inflammatory and catabolic cascades in NPCs

(A) The mRNA levels of *Il1a*, *Il1b*, *Il6*, *Ccl2*, *Ccl5*, *Tnf*, *Mmp3*, and *Mmp13* in NPCs. (B)

Representative WB graphs of NLRP3, p-NF- κ B p65, NF- κ B p65, p-STAT3, and STAT3 in

NPCs. (NS: not significant, * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, $n = 5$)

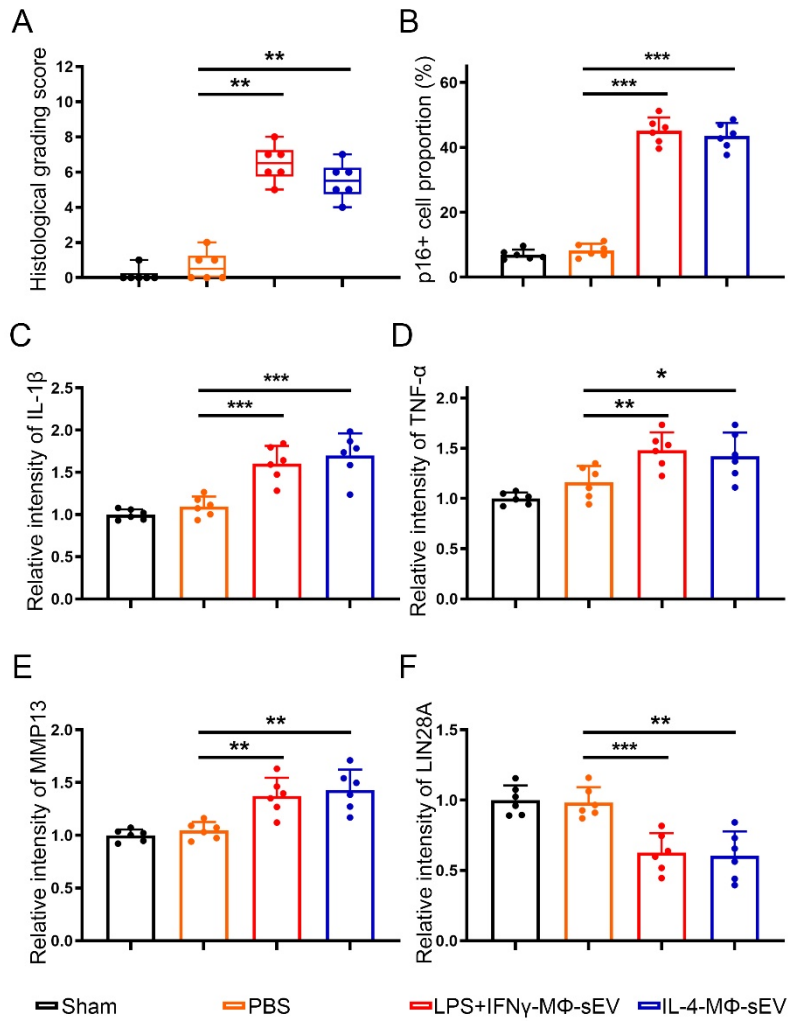


Figure S3: Statistical analyses of histological evaluation

(A) Histological grading scores assessed by HE and SOFG staining. (B-F) Semi-quantitative analyses of the expression levels of p16, IL-1 β , TNF- α , MMP13, and LIN28A in rat coccygeal IVD tissues injected with M Φ -sEVs. (NS: not significant, * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, $n = 6$)

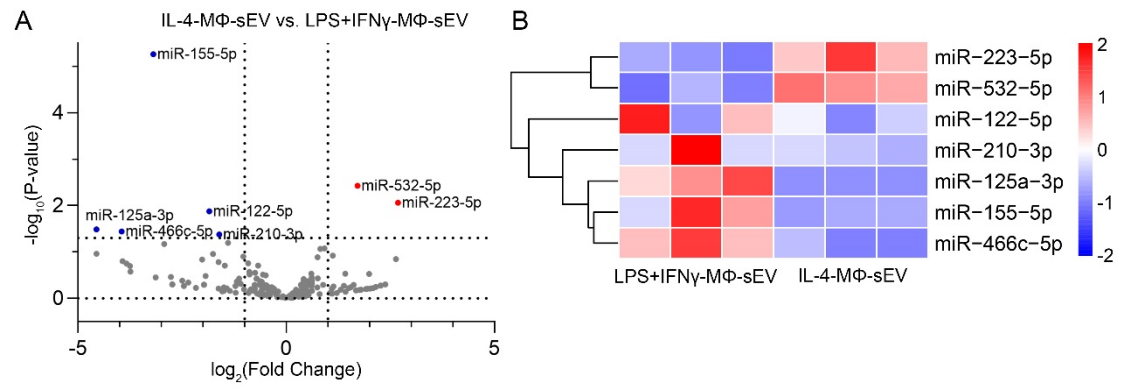


Figure S4: PANDORA-seq analysis of MΦ-sEVs

(A) Volcano Plot of PANDORA-seq of MΦ-sEVs. Red dots represent upregulated miRNAs;

blue dots represent downregulated miRNAs. (B) Heatmap of PANDORA-seq of MΦ-sEVs.

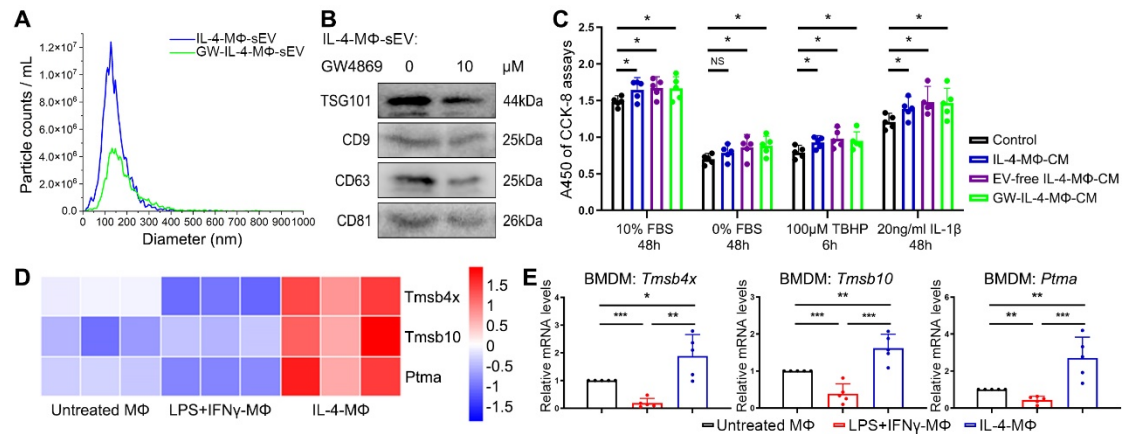


Figure S5: Removal of EVs improved the cytoprotective effects of IL-4-MΦ-CM

(A) The particle concentrations of MΦ-sEVs measured by NTA. (B) Representative WB graphs of TSG101, CD9, CD63, and CD81 in IL-4-MΦ-sEVs. (C) The viability of NPCs measured by CCK-8 assays. (D) Heatmap of RNA-seq of rat BMDMs. Red represents high expression; blue represents low expression. (E) The mRNA levels of *Tmsb4x*, *Tmsb10*, *Ptma* in BMDMs. (NS: not significant, * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, $n = 5$)