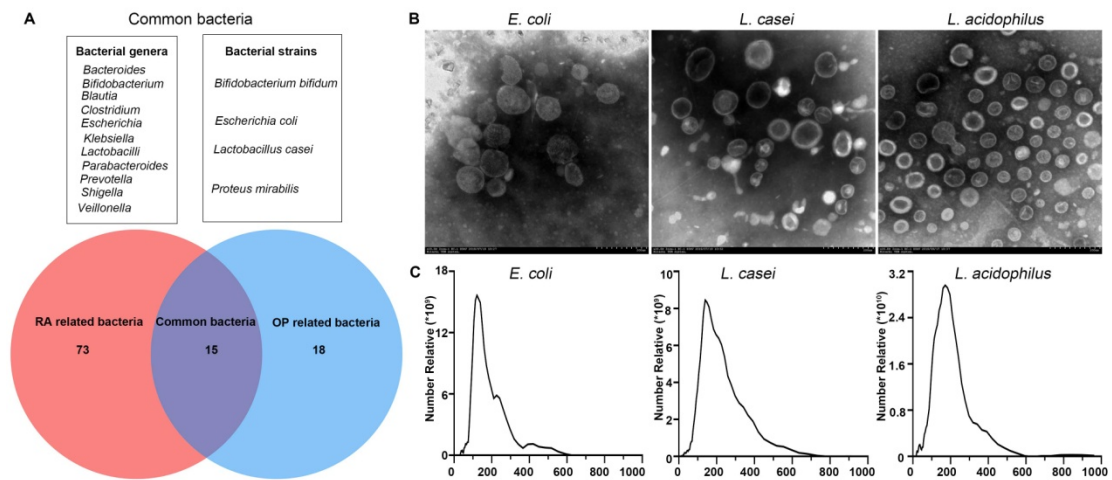


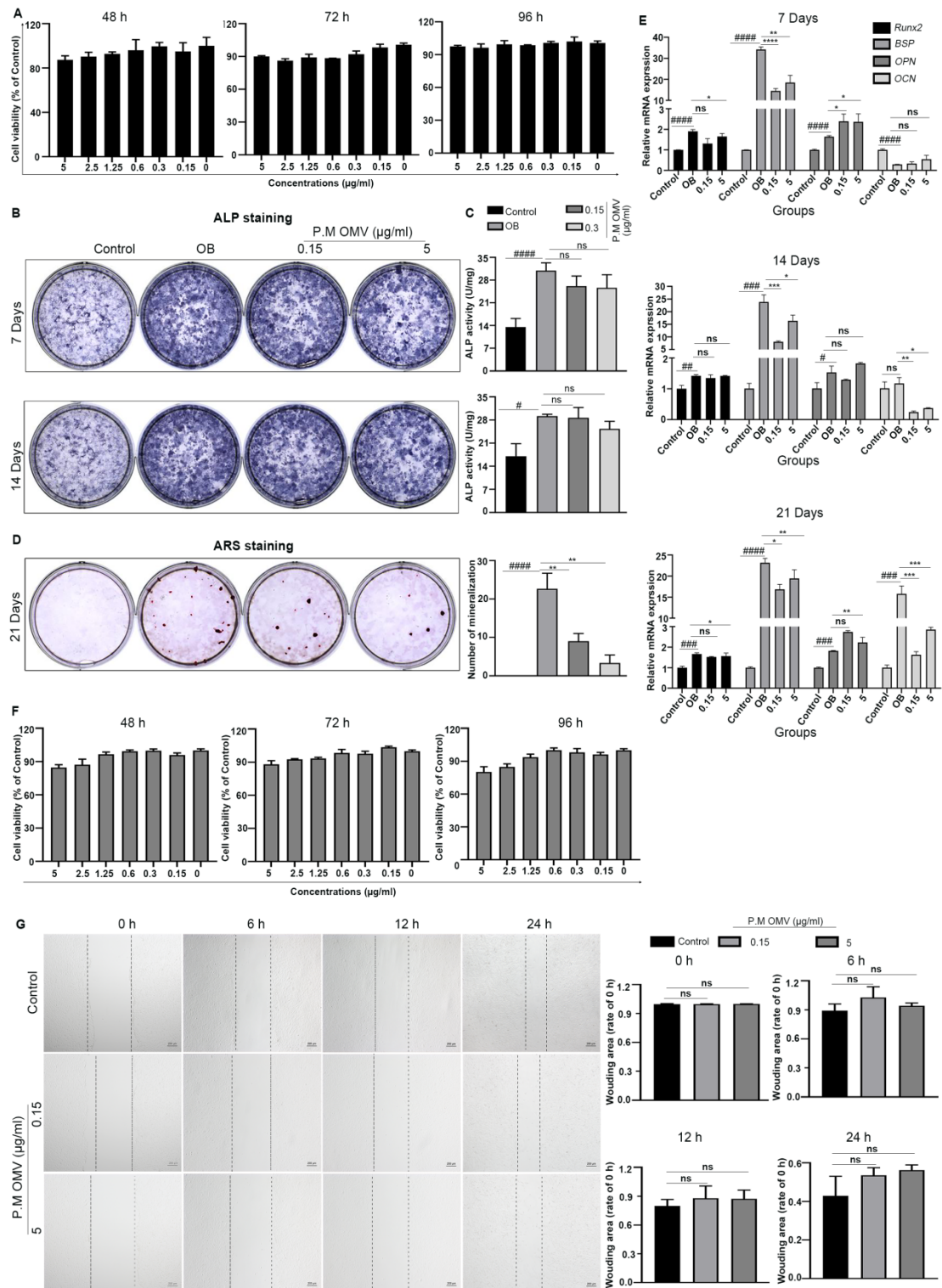
## Supplementary Information

**Supplementary Table 1.** The mRNA sequence list

Genes name	Primer sequence (5'-3') Forward	Primer sequence (5'-3') Reverse
<i>Acp5</i>	TCATGGGTGGTGCTGCT	GCCCACAGCCACAAATCT
<i>MMP9</i>	AAGGCAGCGTTAGCCAGAA	GCGGTACAAGTATGCCTCTGC
<i>CTSK</i>	GTGGATGAAATCTCTCGGCGT	CACTGGTCAT GTCTCCCAAGT
<i>NFATc1</i>	TGTTGCTCTGGGGTGTATC	CATGTGCCCTGGAGAGTT
<i>c-Fos</i>	CAGCGAGCAACTGAGAAGA	AAGGGGTCCAGGGGTAG
<i>Itgβ3</i>	CAGTGGCCGGGACAACCTC	GACAAAGTCTCATCTGAGCACCAG
<i>Jdp2</i>	AGAAGGAACGCACAGAGTTTC	TGAGCATCAGGATAAGCTGTTG
<i>Runx2</i>	GCCGGGAATGATGAGAAC	TGGGGAGGATTTGTGAAGA
<i>OCN</i>	CAGTCCCCAGCCCAGAT	GCGTTTGTAGGCGGTCTT
<i>OPN</i>	GAGCGAGGATTCTGTGGA	TCGACTGTAGGGACGATTG
<i>BSP</i>	AAGCAGGTGCAGAAGGAA	GCGAGGTGGTCCCATAG
<i>Cyc1</i>	ACATCGTTTCGAGCTAGGCAT	CTGGGGTGCCATCATCATACT
<i>Uqcr2</i>	GGATCTTGAGTTTACCAAATTACC	AGATGAAGCTCCTTTGGTAGTC
<i>Abca1</i>	CTTCCCACATTTTTGCCTGG	AAGGTTCCGTCCTACCAAGTCC
<i>β-actin</i>	CCTCTATGCCAACACAGTGC	CCTGCTTGCTGATCCACATC

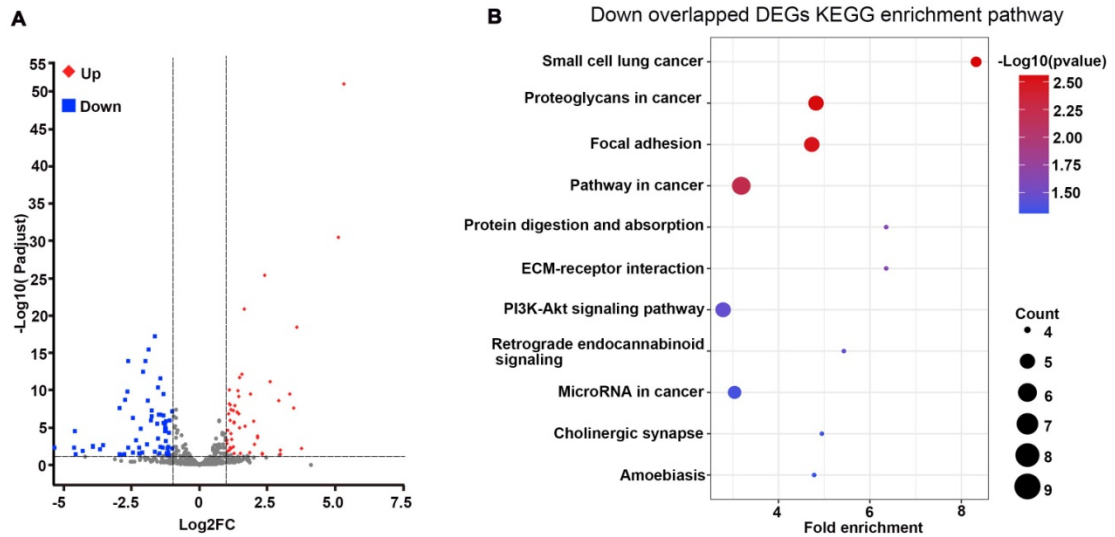


**Supplementary Figure 1. Characterization of OMVs from commonly identified bacteria from RA and OP.** (A) Bacteria shared between rheumatoid arthritis and osteoporosis from MDIDB website. (B) Morphology and (C) size determination of *E. coli*, *L. casei* and *L. acidophilus* by transmission electron microscopy and nanotrack analysis. *E. coli*: *Escherichia coli*; *L. casei*: *Lactobacillus casei*; *L. acidophilus*: *Lactobacillus acidophilus*. Scale bar = 200 nm. Data are from three independent experiments.

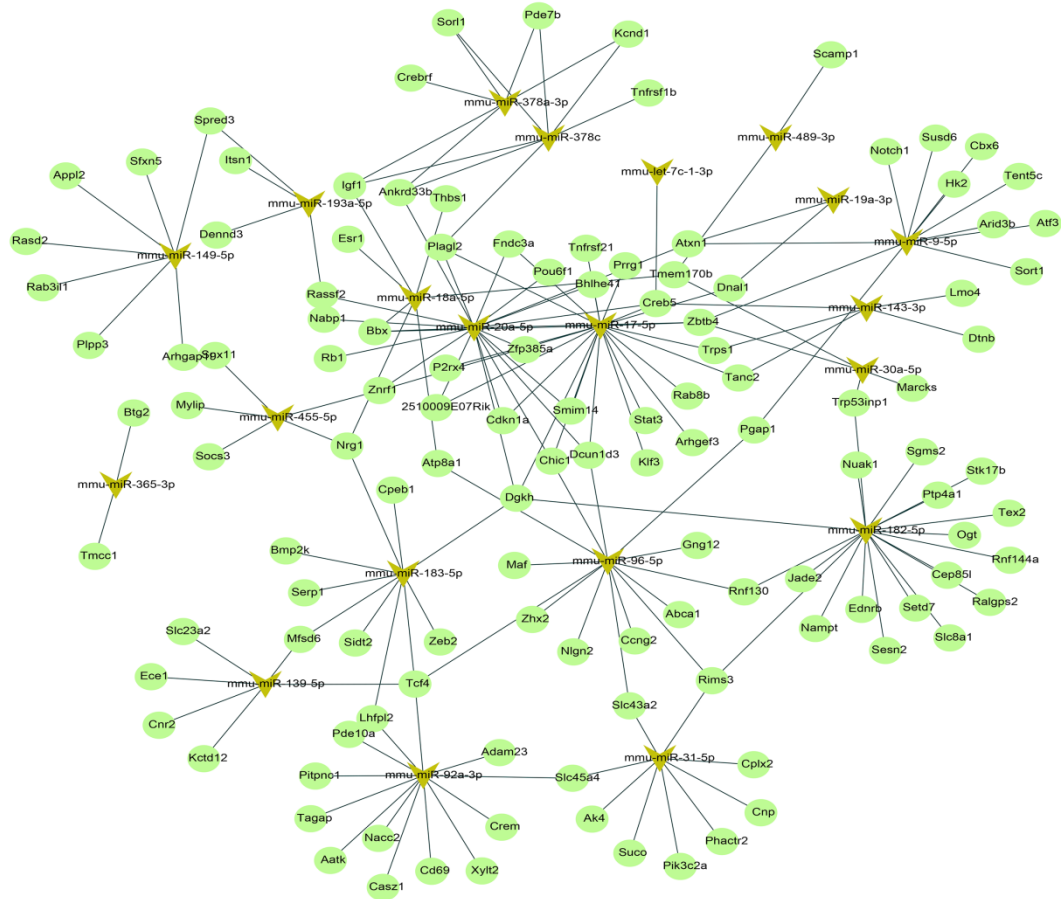


**Supplementary Figure 2. Differential effects of P.M OMVs on osteoblasts and fibroblasts.** (A) P.M OMVs had minimal effect on osteoblast (MC3T3-E1) cell viability, (B-C) ALP activity on day 7 and 14. However, (D) mineralized nodes (alizarin red stain) were significantly affected after 21 days. (E) P.M OMVs differentially affected the expression of OB-related genes (*Runx2*, *BSP*, *OPN* and

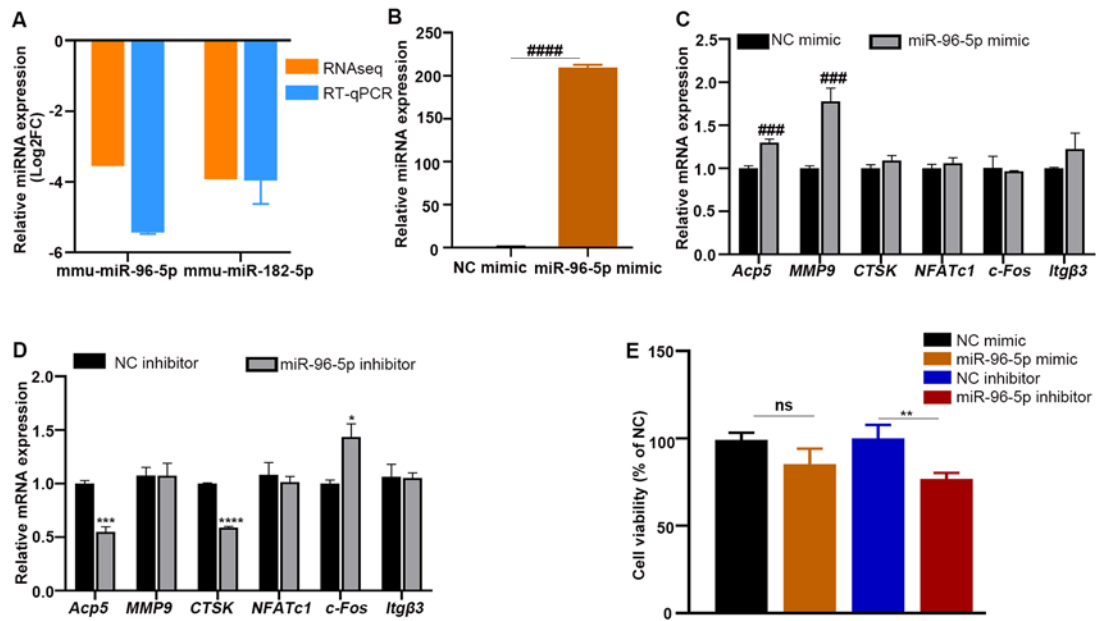
OCN) on various days. Negligible effect of P.M OMVs on (F) cell viability and (G) migration ability of fibroblasts. P.M: *Proteus mirabilis*. scale bar = 200  $\mu$ m. Data are from three independent experiments and represented as mean  $\pm$  SD. #,  $p < 0.05$ ; ##,  $p < 0.01$ ; ###,  $p < 0.001$ ; ####,  $p < 0.0001$  compared to Control. \*,  $p < 0.05$ ; \*\*,  $p < 0.01$ ; \*\*\*,  $p < 0.001$ ; \*\*\*\*,  $p < 0.0001$  to OB. ns, not significant.



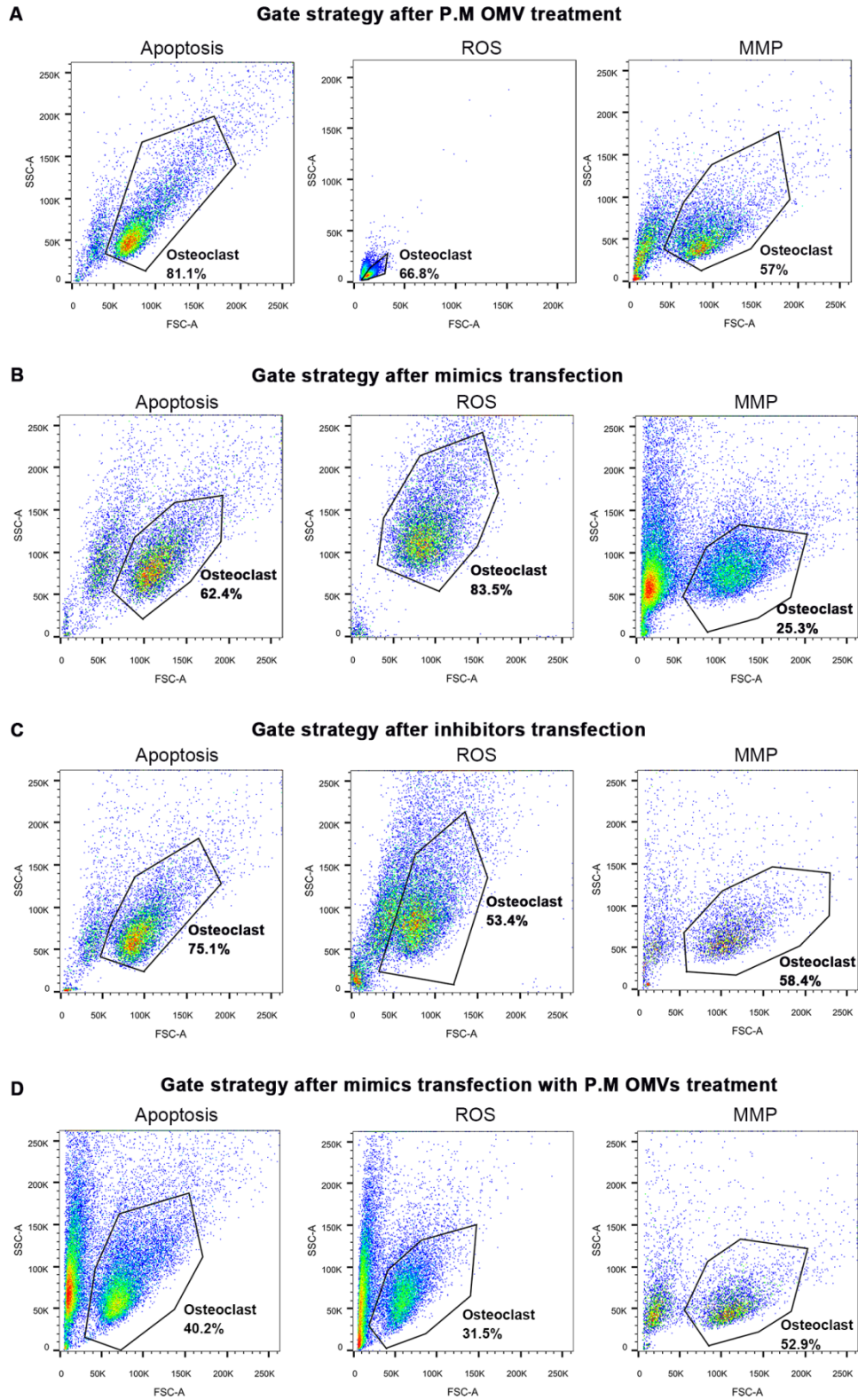
**Supplementary Figure 3. Volcano plot of miRNA and the KEGG enrichment analysis of overlapped DEGs.** (A) Volcano plot of miRNA genes altered by RANKL ( $\log_2 \text{FC} \geq 1$ ,  $p < 0.01$ ), (B) KEGG enrichment analysis of down-regulated genes are shown in the bubble chart. The top 15 genes that were significantly enriched in the KEGG pathway ( $p < 0.05$ ) are presented.



**Supplementary Figure 4. The network of down-regulated miRNA-mRNA.** The regulatory network of 177 down- regulated miRNA-mRNA pairs.

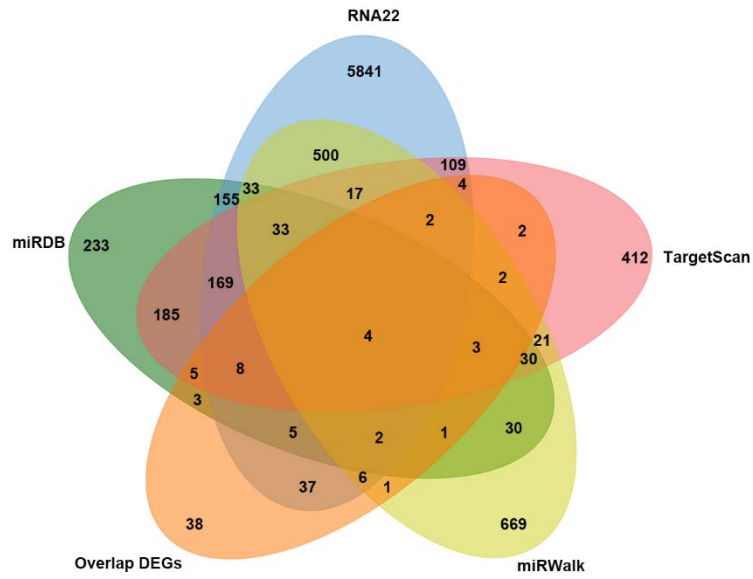


**Supplementary Figure 5. The effect of miR-96-5p on osteoclasts.** (A) Relative miRNA expression from P.M OMVs or RANKL treated groups. (B) Transfection efficiency of miR-96-5p. (C-D) Effect of mmu-miR-96-5p mimic or inhibitor on OC-related genes and (E) osteoclast viability. ###,  $p < 0.001$ ; ####,  $p < 0.0001$  compared to NC mimic. \*,  $p < 0.05$ ; \*\*,  $p < 0.01$ ; \*\*\*,  $p < 0.001$ ; \*\*\*\*,  $p < 0.0001$  compared to NC inhibitor. ns, not significant.

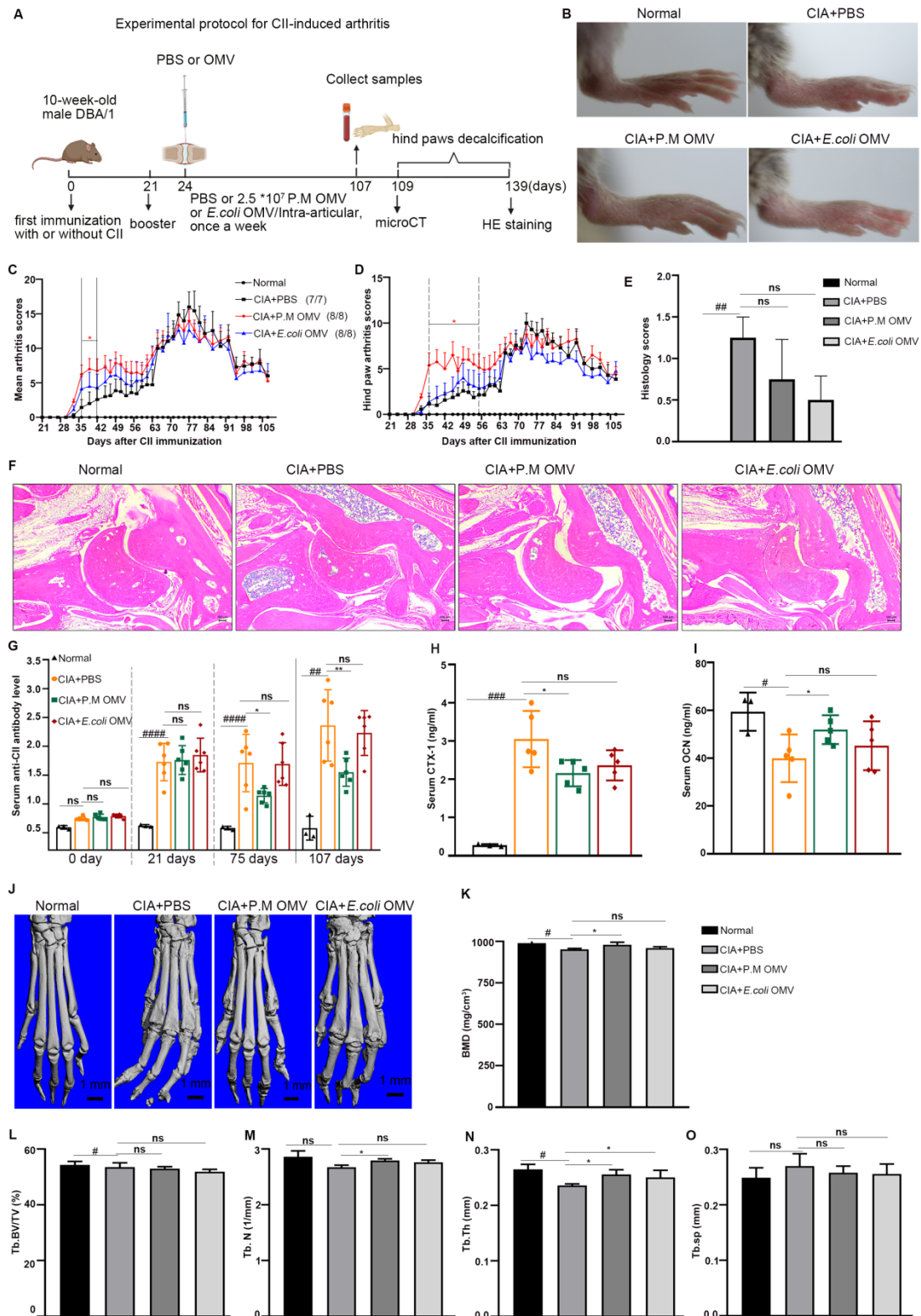


**Supplementary Figure 6. FACS gating strategy.** (A) gating strategy for apoptosis, for ROS and for MMP after P.M OMV treatment and (B) mimics and (C) inhibitor transfection and (D) mimics transfection with P.M OMVs treatment.





**Supplementary Figure 7. Prediction of miR-96-5p target genes.** The intersection of mmu-miR-96-5p target genes predicted by TargetScan, RNA22, miRDB and miRWalk with the overlapped target DEGs of miR-96-5p from RNAseq data.



**Supplementary Figure 8. Effect of P.M OMVs on inflammation and bone erosion in CIA.** (A) Experimental protocol. (B) Representative pictures of hind paws of mice from different groups. (C-D) Mean arthritis and hind paw arthritis scores from each group after booster immunization. (E-F) HE staining of paw sections on day 107. (G) Serum anti-CII antibody levels in each group on days 0, 21, 75 and 107 (normal group

n = 3, other groups n = 5). Serum **(H)** CTX-1 and **(I)** OCN levels. **(J)** Representative images of hind paws after  $\mu$ CT (n = 3). **(K-O)** Analysis of bone parameters in different groups. n, indicates number of mice. BMD: bone marrow density, Tb.BV/TV: trabecular bone volume per tissue volume, Tb.N: trabecular number, Tb.Sp: trabecular separation and Tb.Th: trabecular thickness.. Arthritis scores are represented as mean  $\pm$  SEM, and the remaining data are given as mean  $\pm$  SD. #, p < 0.05; ##, p < 0.01, ###, p < 0.001, ####, p < 0.0001 compared to Normal; \*, p < 0.05; \*\*, p < 0.01 compared to CIA. ns, not significant.