

(A) Genotyping of MSR1 WT or MSR1 KO mice was confirmed by PCR of DNA

samples from tail chips.





(A) Flow cytometry was used to identify the phenotype profile of BMSCs (positive makers: CD90, CD73 and CD105; negative makers: CD45, and CD34), and the

representative results are shown.

(B) Staining with alizarin red, oil red O, alcian blue was performed to test the osteogenic, adipogenic, and chondrogenic differentiation of BMSCs, respectively.

(C) Immunoblot images showing the expression patterns of MSR1 in BMDMs and BMSCs.

(D) The knockout efficiency of MSR1 in macrophages was confirmed by qPCR and Western blotting. Values are mean \pm SD, ***p < 0.001.

(E) As shown in the schematic of co-culture cell migration assay, BMSCs were seeded in the upper chamber, and macrophages were cultured in the lower chamber.

(F and G) MSR1 did not affect the migration of BMSCs in vitro. Migration ability of BMSCs co-cultured with non-activated or LPS-activated BMDMs from MSR1 WT or KO mice was detected (F). Quantification of migrated cells (G). Values are mean \pm SD, ns indicates no significance.

(H) mRNA expression levels of osteogenic marker genes (Col1, ALP, Ocn and Runx2) in osteogenic differentiation of BMSCs on day 7 using qPCR in different groups. β -actin was used as an internal control in this study (Values are mean ±SD, *p < 0.05, **p < 0.01).

(I) Overexpression efficiency of MSR1 in RAW264.7 cells was confirmed by qPCR and Western blotting. Values are mean \pm SD, ***p < 0.001, ns indicates no significance.

(J) mRNA expression levels of Col1, ALP, Ocn and Runx2 in osteogenic differentiation of BMSCs on day 7 were detected by qPCR in different groups. β -actin

was used as an internal control (Values are mean \pm SD, *p < 0.05, **p < 0.01, ***p < 0.001, ns indicates no significance).



(A) Infiltration of F4/80+ macrophages was detected on day 7 post-surgery in the tibial monocortical defect model from MSR1 WT and KO mice, (Values are mean \pm SD, ns indicates no significance). iNOS group indicates the samples stained with anti-F4/80 and anti-iNOS; the slides stained with anti-F4/80, and anti-CD206 denote the CD206 group.

(B) Tartrate-resistant acid phosphatase staining (TRAP) staining was used to detect the number of osteoclasts in fracture tissues of the tibial monocortical defect model on day 7 post-surgery (Values are mean \pm SD, ns indicates no significance).



Figure S4

(A and B) mRNA expression levels of M1-like marker genes (iNOS and IL-1b) (A) and M2-like marker genes (CD206 and CD163) (B) in MSR1 WT BMDMs with or without co-culture at indicated time-points (24, 48, and 72 h) were detected by qPCR. Values are mean \pm SD, *p < 0.05, **p < 0.01, ***p < 0.001, ns indicates no significance.

(C) mRNA expression levels of M1-like marker genes (iNOS and IL-1b) in MSR1WT and KO macrophages with or without co-culture were detected by qPCR. Values

are mean \pm SD, *p < 0.05, **p < 0.01, ns indicates no significance.

(D) IF staining results of MSR1 WT and KO macrophages without co-culture for M1 marker (iNOS) and M2 marker (CD206). Bar = $50 \mu m$.

(E) Flow cytometry analysis of MSR1 WT or KO macrophages cultured alone. Dot plots represent F4/80 and iNOS staining of macrophages (left panel), and F4/80 and CD206 staining of macrophages (right panel).

(F) OCR of BMDMs in MSR1 WT or KO group without co-culture was detected using a Seahorse Bioscience XFp analyzer. O: Oligomycin, F: Carbonyl cyanide 4-(trifluoromethoxy)phenylhydrazone (FCCP), A&R: antimycin A/rotenone.

(G) IF staining results of MSR1 WT BMDMs in indicated groups for the M2-like marker (CD206). Bar = $50 \mu m$.

(H) mRNA expression levels of M2 marker genes (CD206 and CD163) in MSR1 WT BMDMs in different groups were detected by qPCR. Values are mean \pm SD, **p < 0.01, ***p < 0.001.



(A) OCR of blank (BL), vector (Vec) and MSR1-overexpression (OE) RAW264.7 cells without co-culture was evaluated using a Seahorse Bioscience XFp analyzer.

(B) IF staining results of BL, Vec, and MSR1-OE RAW264.7 cells without co-culture for the M1-like marker (iNOS) and M2-like marker (CD206). Bar = $50 \mu m$.

(C) mRNA expression levels of M1-like macrophage marker genes (iNOS and IL-1b) in indicated groups were tested by qPCR. Values are mean \pm SD, *p < 0.05, **p < 0.01, ns indicates no significance.

(D) Flow cytometry analysis of RAW264.7 cells from different groups without co-culture. Dot plots represent F4/80 and iNOS staining of RAW264.7 cells, and F4/80 and CD206 staining of RAW264.7 cells.



Figure S6

(A) Immunoblot images showing the effect of macrophage MSR1 KO or OE on the expression of p-AKT/AKT and p-GSK3β/GSK3β without co-culture.

(B and C) Distribution of β -catenin (green) in MSR1 WT and MSR1 KO BMDMs (B), and MSR1 BL, Vec, and OE RAW264.7 cells (C) without co-culture were analyzed by cell IF staining. The cell nuclei were stained with DAPI (blue fluorescence), Scale bars: 50 μ m.

(D) Immunoblot images showing the role of MSR1 KO or OE cultured alone on the expression of β -catenin from nuclear and whole-cell lysates.



🗖 WT

Figure S7

Mitochondrial biogenesis related genes

Log2 (Fold change)

-4.05

0.23 -0.06

-0.06

Gene

nrf1

esrra

ppargc1a (PGC1a)

ppargc1b (PGC1 β)

Е

(A) Log2 (fold change) value of several pro-osteogenic differentiation cytokines (FGF7, TGFB2, IGFBP5, IGF2, BMP4, BMP5, BMP6, and FGF20) based on RNA-sequencing.

(B) mRNA expression levels of osteoinductive factors (FGF7, TGFB2, IGFBP5, IGF2, BMP4, BMP5, BMP6, and FGF20) in MSR1 WT and MSR1 KO BMDMs (upper panel), and MSR1 BL, Vec, and MSR1 OE RAW264.7 cells (lower panel) were determined by qPCR. Values are mean \pm SD, *p < 0.05, **p < 0.01, ***p < 0.001, ns

indicates no significance.

(C) mRNA expression levels of osteogenic markers (Col1, ALP, Ocn and Runx2) in osteogenic differentiated BMSCs at day 7 were detected by qPCR in different groups. β -actin was used as an internal control. Values are mean \pm SD, *p < 0.05, **p < 0.01, ***p < 0.001.

(D) mRNA expression levels of Col1, ALP, Ocn and Runx2 in osteogenic differentiated BMSCs on day 7 were detected by qPCR in the indicated groups. β -actin was used as an internal control. Values are mean \pm SD, *p < 0.05, **p < 0.01, ***p < 0.001, ns indicates no significance.

(E) Log2 (fold-change) values of mitochondrial biogenesis related genes (PGC1α, PGC1β, Nrf1 and Esrra) based on RNA-sequence.



(A) Representative 2D coronal images of injured tiblae from different transplanted mice (KO to KO vs. WT to KO) on 7 or 14 days post-injury.

(B) The infiltration of F4/80+ macrophages in different groups were determined on 7 days post-surgery in tibial monocortical defect model from different transplanted mice (KO to KO vs. WT to KO) (Values are mean \pm SD, ns indicates no significance). iNOS group indicates the samples stained with anti-F4/80 and anti-iNOS; the slides stained with anti-F4/80, and anti-CD206 denote the CD206 group.

Supplementary Table 1

The sequences of primers, wild-type and mutant PGC1a promoter region				
	The primer sequences for qPCR			
Mouse	sense 5'-3'	antisense 5'-3'		
MSR1	TGGAGGAGAGAATCGAAAGC	CTGGACTGACGAAATCAAGG		
	А	AA		
RUNX2	AGAGTCAGATTACAGATCCCA	TGGCTCTTCTTACTGAGAGAG		
	GG	G		
OCN	ATGAGCCCTCAGACTCCTC	CGGCCGTAGAGCGCCGATA		
ALP	CCAACTCTTTTGTGCCAGAGA	GGCTACATTGGTGTTGAGCTT		
ALF		TT		
Col1	CTGGCGGTTCAGGTCCAAT	TTCCAGGCAATCCACGAGC		
iNOS	CAGGAGGAGAGAGATCCGAT	GCATTAGCATGGAAGCAAAG		
INOS	TTA	А		
IL-1β	TGGAAAAGCGGTTTGTCTTC	TACCAGTTGGGGGAACTCTGC		
CD206	CTTCGGGCCTTTGGAATAAT	TAGAAGAGCCCTTGGGTTGA		
CD163	GGTGGACACAGAATGGTTCTT	CCAGGAGCGTTAGTGACAGC		
CD105	С	CCAGGAGCGITAGIGACAGC		
PGC1a	TATGGAGTGACATAGAGTGTG	GTCGCTACACCACTTCAATCC		
	СТ			
IGF2	GTGCTGCATCGCTGCTTAC	CGGTCCGAACAGACAAACTG		

	CCCTGCGACGAGAAAGCTC	GCTCTTTTCGTTGAGGCAAAC
IGFBP5		С
D 4	TTGATACCTGAGACCGGGAA	ACATCTGTAGAAGTGTCGCCT
Bmp4	G	С
	TTACTTAGGGGTATTGTGGGC	
Bmp5	Т	TGAACGTGATTGTCTCCCAAG
	GCGGGAGATGCAAAAGGAGA	ATTGGACAGGGCGTTGTAGA
Bmp6	Т	G
5057	TGGGCACTATATCTCTAGCTT	
FGF7	GC	GGGTGCGACAGAACAGTCT
ECEO	AGGATCACAGTCTCTTCGGTA	GTCATTCATCCCAAGGTACAG
FGF20	TC	G
TCEDO		GCAGGGGCAGTGTAAACTTAT
TGFB2	CTTCGACGTGACAGACGCT	Т
0		CCAGTTGGTAACAATGCCATG
β-actin	GGCTGTATTCCCCTCCATCG	Т

The primer sequences for the ChIP assay			
	sense 5'-3'	antisense 5'-3'	
D1	AATGTGTGGCCGAACACACTG	TTGTTAGTTGCTCACCAACCT	
P1	TAGA	TGGA	
P2	TTTAAATTCTCTTGAGAAGAG	TGCTTAAAACAGCCACTCTGT	

	CAAA	ССТС
P3	GATCATTAGCTTCATGGATGT	TAACTGATACTTTGGTTTCTCT
F3	GCTG	TTG
P4	CCATCAGGATGCCAGGATTGC	TCCAAACATCAGAAAGGTATT
P4	TTGA	ATTC
P5	AGAGGACAGTTGTAGCAGTG	TCTGACTTTATATAGTCAGTT
F.J	AAGTA	АСТА
P6	CTGAGAGAAGTCACCAATGTT	TAACCAACTCTCAGCACTTTC
ro	TTCC	САТА
P7	TGTCCTCTGTCTGTAATGTCA	CAGCTTAGCTACTCACCTGCC
17	CAGG	CCCA
P8	TTTCAGGGATGGCAGCAGCA	СТТТСТТТСТТТСТТТСТТТСТТ
10	ATTGT	ТС
P9	AAAGAAACAAAGAAAGAAAG	AAAACAGGCAAATAGCAAAG
1.2	AAAGA	ATCCC
P10	GGATGGAAAATAAATTTAAA	AAAGCTATTAAAAAGTAGGC
F IU	ААААА	TGGGC

The sequence of wild-type and mutanted promoter region of PGC1 α			
	wild-type	mutation	
-1250 —	gggttaagtctgagcacccaagtgttatggaaag	gggttaagtctgagcacccaagtgttatggaaag	
-1201	tgctgagagttggtta	tgctgagagttggtta	

-1151gcacctgcattacccgtgaacgcattaccc1150ctcattgactcaggaacgacaaaaaagtattagtaagcaaagctcaagaa-1101aagcaaagctcaagaaaagcaaagctcaagaa1100atgagtatctctgctgataccatttcagtgtttttcctatgagtatctctgctgataccatttcagtgtttttcct-1051tcattccctggatcattccctgga1000gtcaatggttggaggcactagggttggaggcactagggttggaggcactagggttgga1000gtcaatgtttattcaaaaaagcaccctgaagccgtcaatgtttattcaaaaaggcaccctgaagcc-951atgaggaagactgtgcatgaggaagactgtgc-950tacatatgagaaaagaaataaggggtgggggctacatatgagaaaagaaataaggggtgggggc-901aggtgagtagctaagctgaggtgagtagctaagctg-900tttcagggatggcagcagcaaatgtatttttctagctttcagggatggcagcagcaattgtattttctagc-851atttgttttctgggagccctatgggttgga-850gcctatgggttggtgaacccaagagtctagg-800gtgtgtggcttgcttgcttgcttgcttgcttgcttgctt		1	1
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(Highlight areas are the mutation

sequences)