**Parishin A-loaded Mesoporous Silica Nanoparticles Modulate Macrophage Polarization to Attenuate Tendinopathy**

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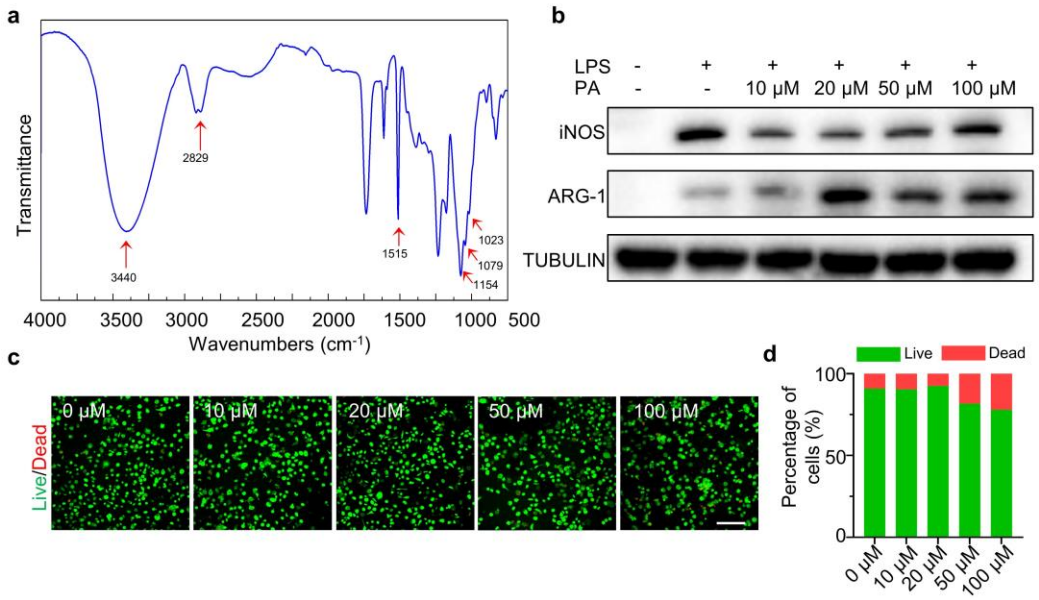
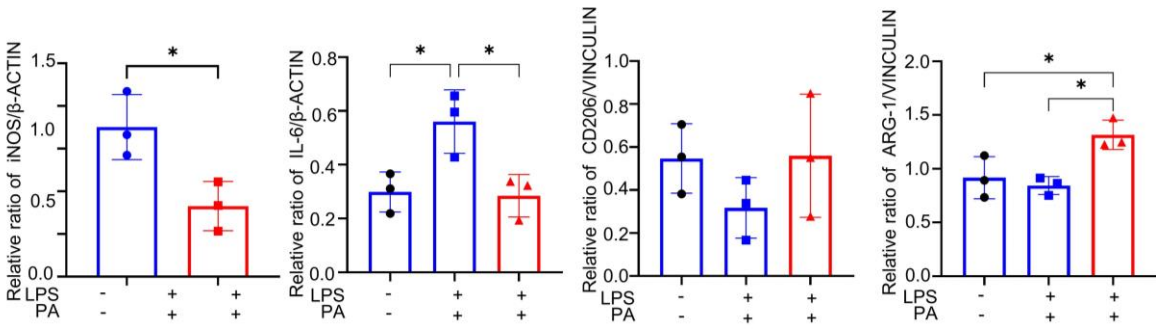
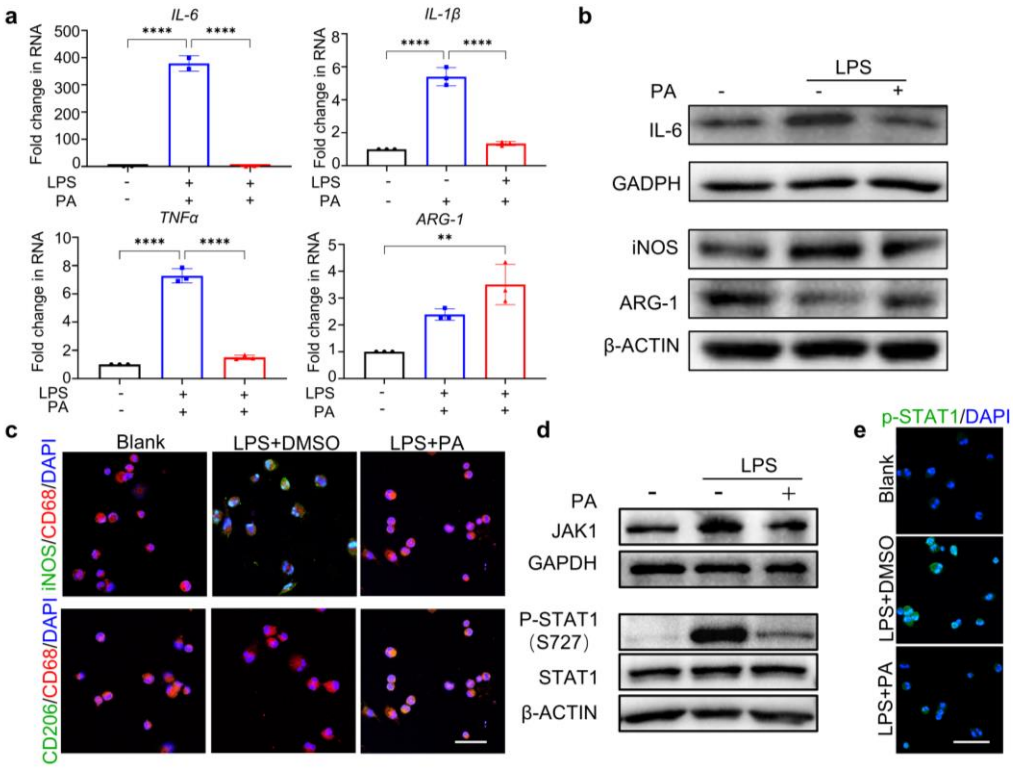


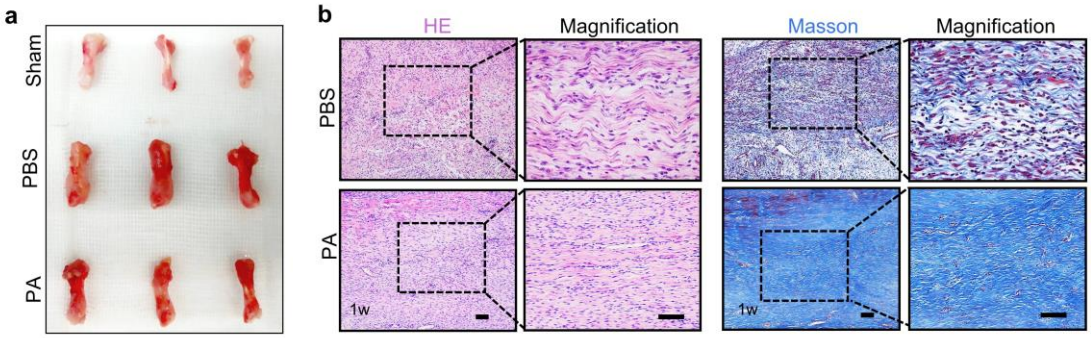

**Supplementary Figure 1. Chemical structure and effective concentrations of PA.** **a** Fourier translation infrared spectroscopy (FTIR) spectra of PA. **b** Western blotting of iNOS and ARG-1 in and PA-treated human THP-1 cells at the concentration of 0, 10 μM, 20 μM, 50 μM and 100 μM. Scale bar, 200 μm. **c** Live/Dead staining of BMDMs treated with dose-dependent PA for 48 h. **d** Semi-quantification of (**c**).



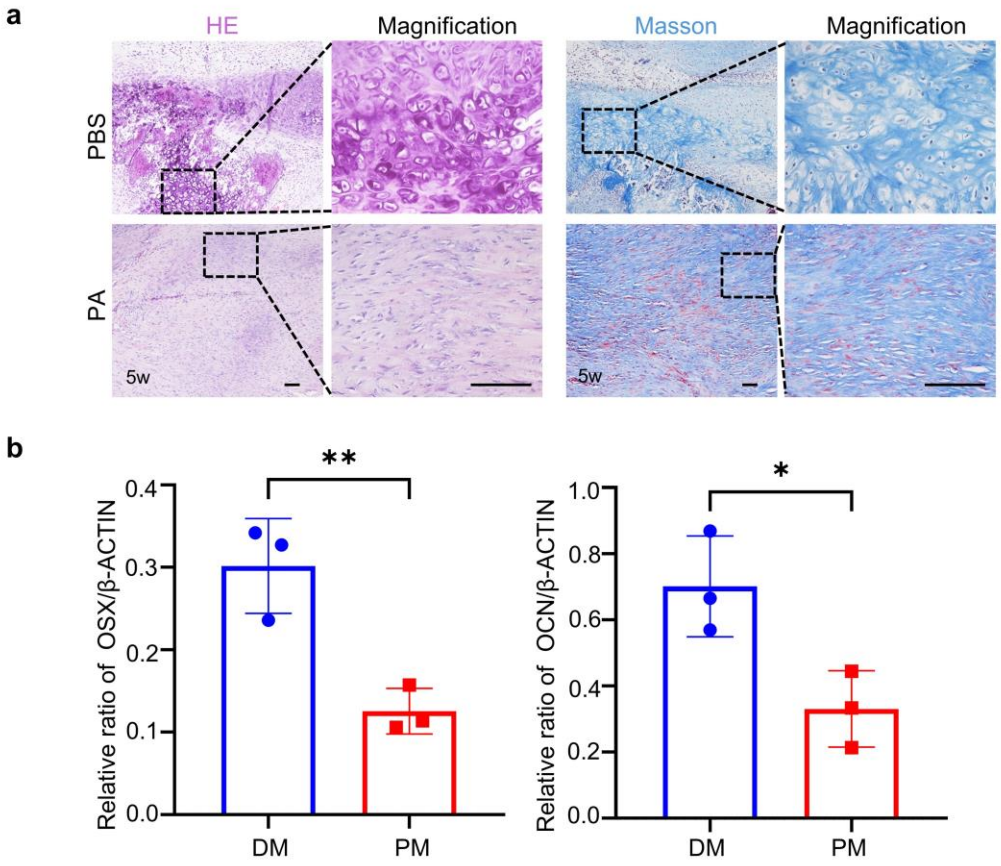

**Supplementary Figure 2. Semi-quantification of Western blots in Figure 1b.** Data are presented as mean ± SD. * $p < 0.05$, *n* =3.



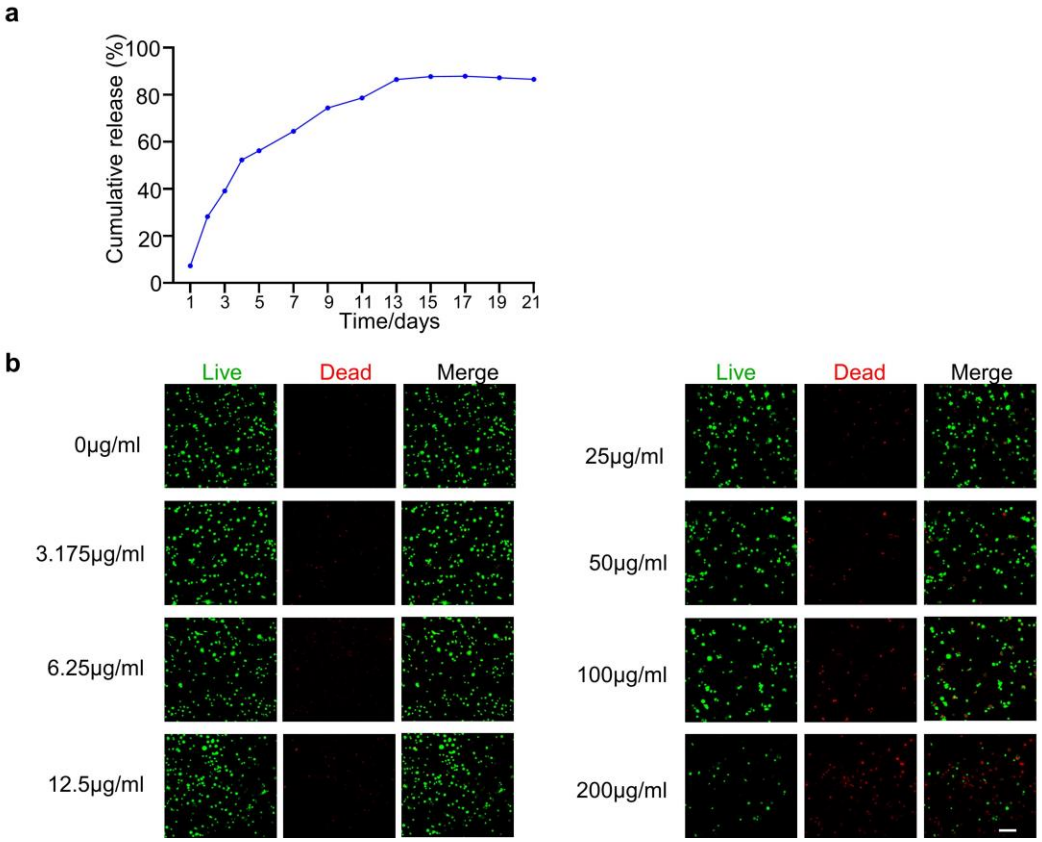

**Supplementary Figure 3. The regulatory role of PA on human THP-1 derived macrophage polarization and the mechanisms. a** RT-PCR of *IL-6*, *IL-1β*, *TNF-α* and *ARG-1* expression in DMSO- and PA-treated human THP-1 cells under LPS stimulation. **b** Western blotting of iNOS, IL-6, and ARG-1 in DMSO- and PA-treated THP-1 cells under LPS stimulation. **c** Co-immunofluorescence staining of iNOS/CD68 and CD206/CD68 in unstimulated THP-1 cells and DMSO, PA-treated THP-1 cells under LPS stimulation. Scale bar, 50 μm. **d** Western blotting of total JAK1, phosphorylation of STAT1 and total STAT1 in DMSO- and PA-treated THP-1 cells under LPS stimulation. **e** Immunofluorescence staining of p-STAT1 in DMSO- and PA-treated THP-1 cells under LPS stimulation. Scale bar, 100 μm. Data are presented as mean ± SD. ** $p < 0.01$ and **** $p < 0.0001$, $n = 3$.



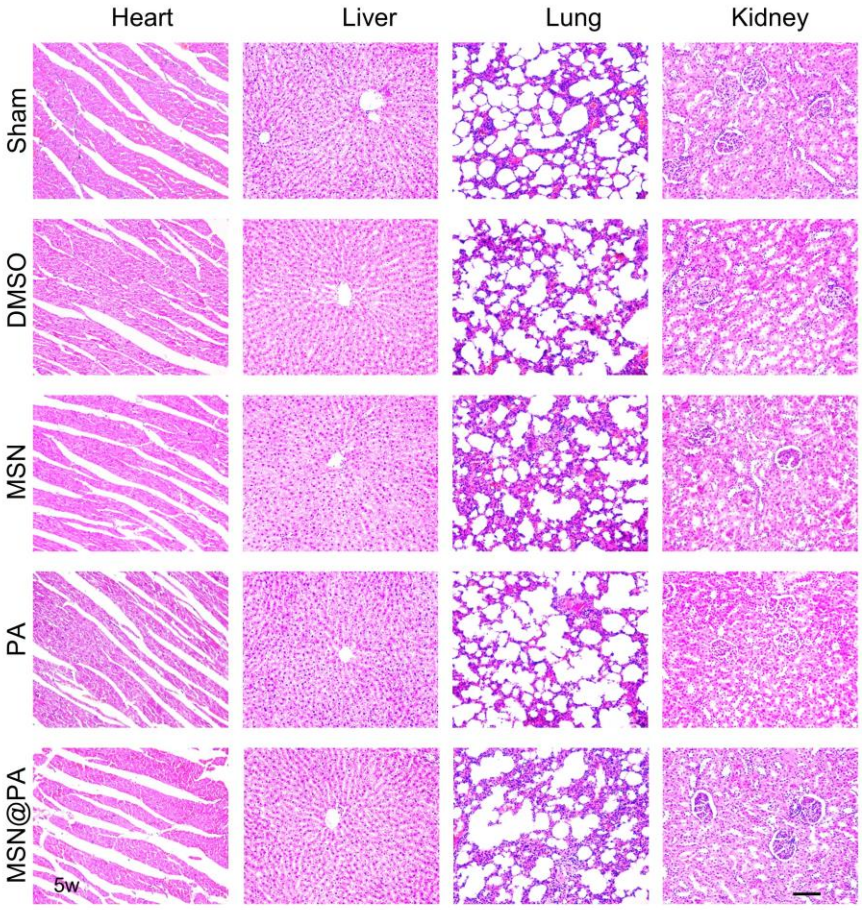

**Supplementary Figure 4. PA alleviates excessive inflammatory response in the early stage of tendon healing. a** Gross view of tendon on 1 week of post-injection. **b** HE and Masson's trichrome stainings of neo-tendons from PBS and PA groups at 1 week. Scale bar, 100 μm.



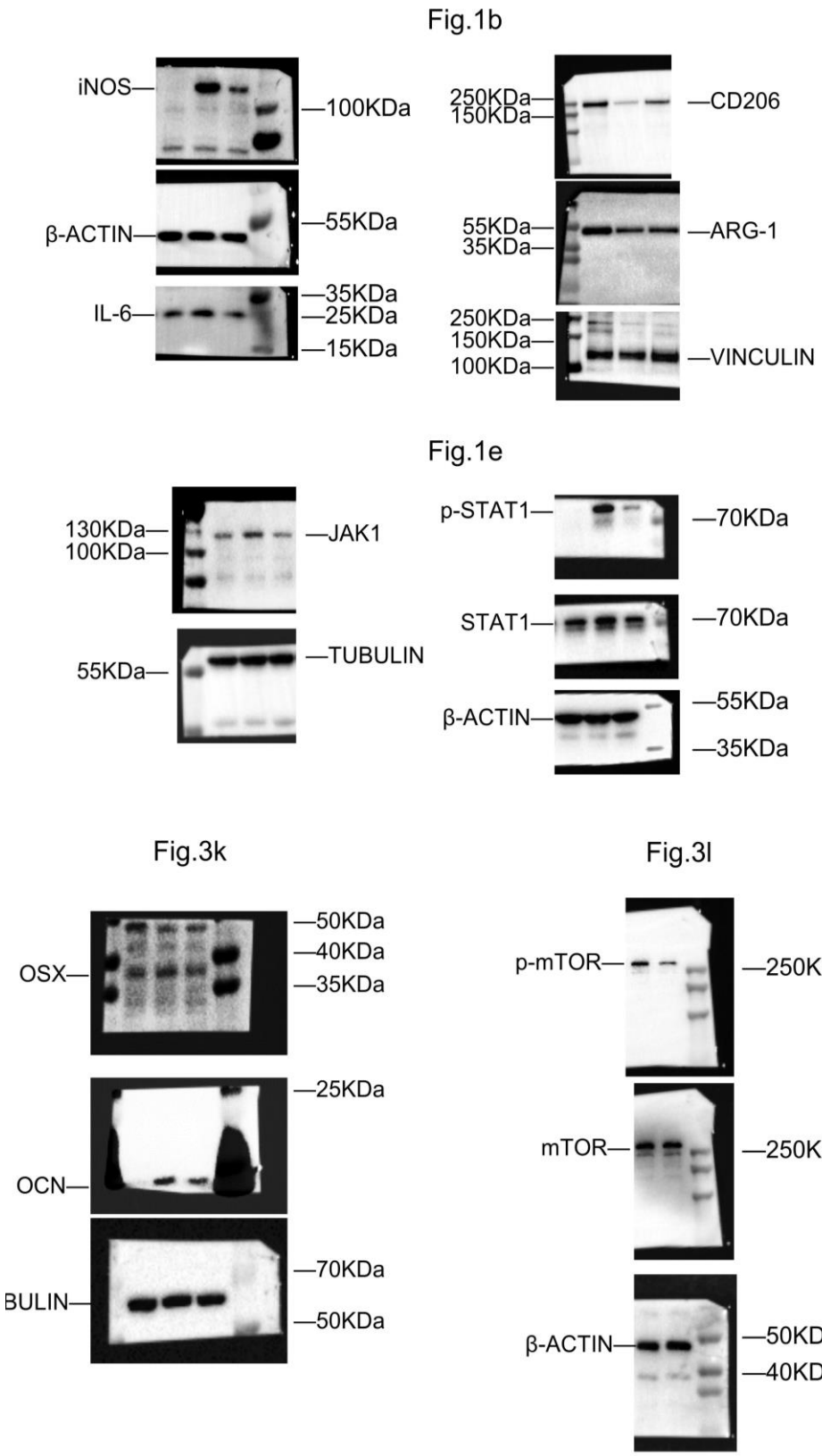

**Supplementary Figure 5. PA prevents tendon heterotopic ossification. a** HE and Masson's trichrome stainings of region of heterotopic ossification from PBS and PA groups at 5 weeks. Scale bar, 100 μm. **b** Semi-quantification of Western blots in Figure 3k. Data are presented as mean ± SD. * $p < 0.05$ and ** $p < 0.01$, $n$ =3.



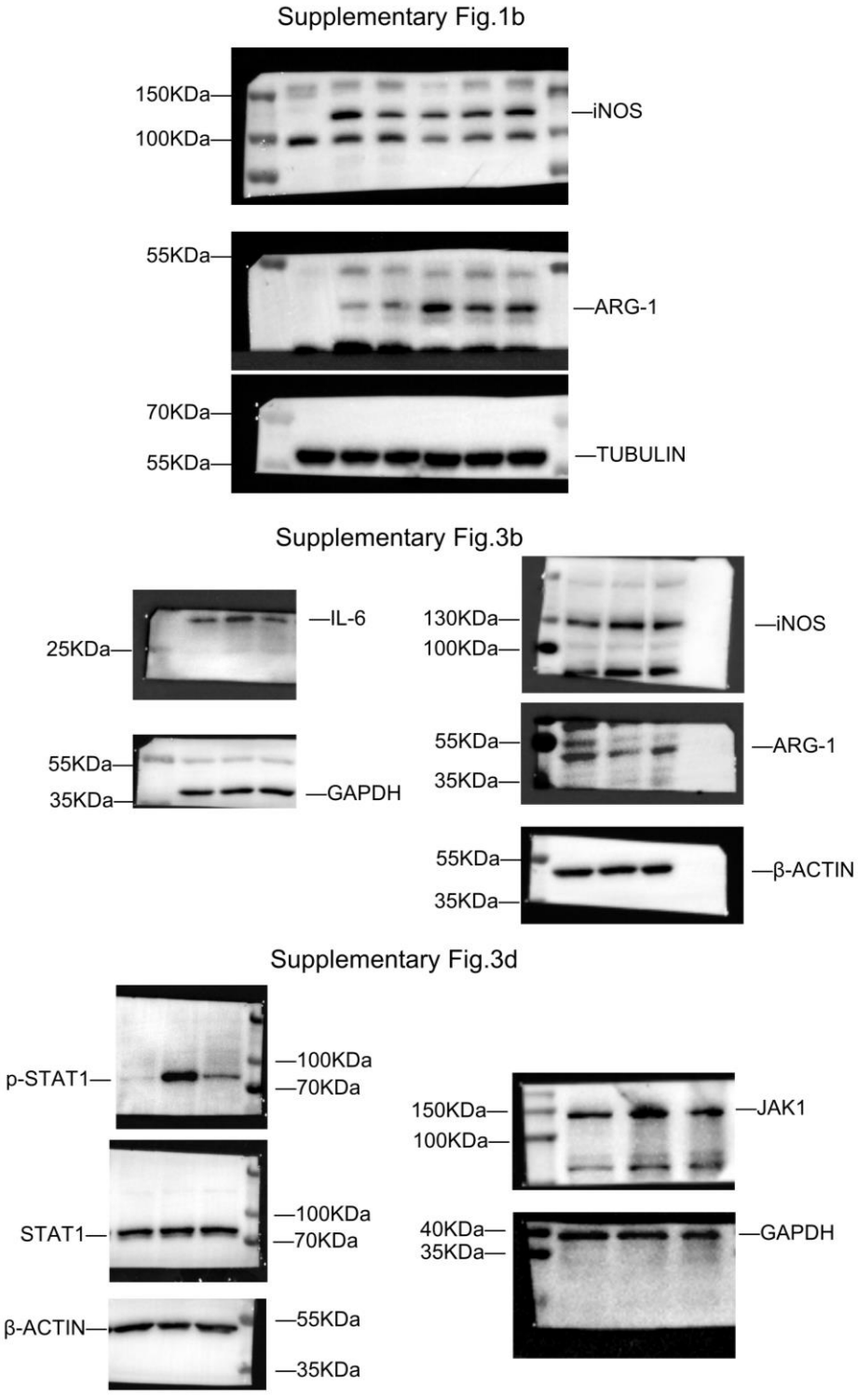

**Supplementary Figure 6. Sustained-release performance and *in vitro* cytotoxicity of MSN. a** Cumulative release concentration curve of PA from MSNs in PBS solution. **b** Live/Dead staining of BMDMs treated with dose-dependent the MSNs for 24 h. Scale bar, 200 μm.




**Supplementary Figure 7. The biological safety of MSN@PA.** HE staining results of representative tissue sections of rats (heart, liver, lung, and kidney) after injection of MSN, PA and MSN@PA. Scale bar, 100 μm.




**Supplementary Figure 8. Original scans of the blots in Fig. 1b, 1e, 3k, 3l.**




**Supplementary Figure 9.** Original scans of the blots in Supplementary Fig. 1b, 3b, 3d.

**Supplementary Table 1. Modified Movin score of tendons from the PBS and PA groups.**

| Variable | PBS group ($n$ = 6) | PA group ($n$ = 6) |
|---|---|---|
| Fiber structure | 2.667 ± 0.516 | 1.500 ± 0.547** |
| Fiber arrangement | 2.883 ± 0.408 | 1.667 ± 0.516** |
| Rounding of nuclei | 2.500 ± 0.547 | 1.333 ± 0.516** |
| Regional variations of cellularity | 2.667 ± 0.516 | 1.667 ± 0.816 |
| Increase in vascularity | 2.500 ± 0.547 | 1.667 ± 0.516** |
| Decreased collagen stainability | 2.667 ± 0.516 | 1.167 ± 0.408** |

Note: Values are Mean ± SD*; **: P* < 0.01 *versus* PBS group.

**Supplementary Table 2. Modified Movin score of tendons from the MSN, PA and MSN@PA groups.**

| Variable | MSN group ($n$ = 6) | PA group ($n$ = 6) | MSN@PA group ($n$ = 6) |
|---|---|---|---|
| Fiber structure | 2.883 ± 0.408 | 1.667 ± 0.516** | 1.333 ± 0.516*** |
| Fiber arrangement | 2.883 ± 0.408 | 2.000 ± 0.633 | 1.500 ± 0.837** |
| Rounding of nuclei | 2.667 ± 0.516 | 1.667 ± 0.816 | 1.500 ± 0.837* |
| Regional variations of cellularity | 2.500 ± 0.837 | 1.667 ± 0.816 | 1.000 ± 0.633* |
| Increase in vascularity | 2.500 ± 0.837 | 1.833 ± 0.753 | 1.333 ± 0.516* |
| Decreased collagen stainability | 2.667 ± 0.516 | 1.500 ± 0.548* | 1.500 ± 0.837* |

Note: Values are Mean ± SD*; *: $p$* < 0.05 *versus* MSN group, **: $P$ < 0.01 *versus* MSN group, ***: $p$ < 0.001 *versus* MSN group.

**Supplementary Table 3.** List of reagents or resources used in the study.

| REAGENT OR RESOURCE | SOURCE | IDENTIFIER |
|---|---|---|
| Lymphoprep | STEMCELL Technologies | 07811 |
| Recombinant Rat M-CSF | Peprotech | 400-28 |
| Lipopolysaccharides | Sigma-Aldrich | L2880 |
| Recombinant mouse GDF-5 | R&D system | 853-G5 |
| RPMI 1640 medium | Solarbio | 31800 |
| Prishin A | Tsbiochem | 62499-28-9 |
| Dimethyl sulfoxide | Solarbio | D8371 |
| Phorbol 12-myristate 13-acetate | Sigma-Aldrich | 16561-29-8 |
| Phosphate buffered solution | Solarbio | P1020 |
| Live/dead staining kit | Solarbio | CA1630 |
| Sodium pyruvate | Hyclone | SH30239.01 |
| Insulin-Transferrin-Selenium | Thermo Fisher Scientific | 41400045 |
| L-ascorbic acid 2-phosphate | Sigma-Aldrich | A5960 |
| TGF-β | Peprotech | |
| Alcian Blue Stain Kit | Solarbio | G1563 |
| Picro Sirius Red Stain Kit | Abcam | AB150681 |
| Masson's Trichrome Stain Kit | Solarbio | G1340 |
| Alizarin Red S solution | Solarbio | G1450 |
| Safranine O-Fast Green FCF Cartilage Stain Kit | Solarbio | G1371 |
| Mounting Medium with DAPI | ZSGB-BIO | ZLI-9557 |
| Dexamethasone | Sigma-Aldrich | D8893 |
| Dialysis bag | Solarbio | YA1077 |
| DMEM | Hyclone | SH30021.01B |
| Fetal bovine serum (FBS) | Thermo Fisher Scientific | 10099-141 |
| SYBR Green Supermix | Thermo Fisher Scientific | 4385612 |
| Prime Script RT Reagent Kit | Takara | RR037B |
| Trizol Reagent | Thermo Fisher Scientific | 15596026 |
| Trypsin-EDTA | Hyclone | SH30042.01 |

| | | |
|---|---|---|
| b-Glycerophosphate | APEXBIO | 13408-09-8 |
| L-Ascorbic acid | Sigma-Aldrich | A5960 |
| Penicillin/streptomycin | Thermo Fisher Scientific | 15070063 |
| Collagenase Type I | Thermo Fisher Scientific | 17100017 |
| Dispase | Roche | 10269638001 |
| RIPA Buffer | Thermo Fisher Scientific | 89900 |
| Protease/Phosphatase Inhibitor Cocktail | Thermo Fisher Scientific | 87786 |
| Pierce BCA protein assay kit | Thermo Fisher Scientific | 23225 |
| L-Glutamine (200mM) | Thermo Fisher Scientific | 25030081 |
| DAB peroxidase substrate kit | ZSGB-BIO | ZLI-9017 |

**Supplementary Table 4.** List of rat primers used in the study.

| TARGET | FOR QPCR DETECTION | |
|---|---|---|
| *Cd206* | FORWARD | GACAGACGGACGAGGAGTTCATTATAC |
| | REVERSE | CCACCAATCACAACAACACAGTCAAC |
| *Cd163* | FORWARD | TTAGAATCACAGCATGGCACAGGTC |
| | REVERSE | CCACAAGAGGAAGGCAATGAGAAGG |
| *Arg1* | FORWARD | AGAGGAGGTGACTCGTACTGTGAAC |
| | REVERSE | TCTGGCTTATGATTACCTTCCCGTTTC |
| *Il6* | FORWARD | AGTTGCCTTCTTGGGACTGATGTTG |
| | REVERSE | GGTATCCTCTGTGAAGTCTCCTCTCC |
| *Inos* | FORWARD | TCTTGGAGCGAGTTGTGGATTGTTC |
| | REVERSE | AGTGATGTCCAGGAAGTAGGTGAGG |
| *Il1β* | FORWARD | AATCTCACAGCAGCATCTCGACAAG |
| | REVERSE | TCCACGGGCAAGACATAGGTAGC |
| *Il10* | FORWARD | GGCAGTGGAGCAGGTGAAGAATG |
| | REVERSE | TGTCACGTAGGCTTCTATGCAGTTG |
| *Stat1* | FORWARD | TCGCACCTTCGTCCTCTTCCAG |
| | REVERSE | TTCACCAACAGTCTCAGCTTCACAG |
| *β-actin* | FORWARD | ATCGTGGGCCGCCCTAGGCA |
| | REVERSE | TGGCCTTAGGGTTCAGAGGGG |

**Supplementary Table 5.** List of human primers used in the study.

| TARGET | FOR QPCR DETECTION | |
|---|---|---|
| *ARG-1* | FORWARD | TGGACAGACTAGGAATTGGCA |
| | REVERSE | CCAGTCCGTCAACATCAAAACT |
| *IL-6* | FORWARD | TACCCCCAGGAGAAGATTCCA |
| | REVERSE | CCGTCGAGGATGTACCGAATT |
| *IL-1β* | FORWARD | ACCTATCTTCTTCGACACATGGG |
| | REVERSE | GAGGTGGAGAGCTTTCAGTTCAT |
| *TNF-α* | FORWARD | CTGGTATGGACCCATCTATCTGG |
| | REVERSE | CAGGGCAAATGATCCCAAAGTAGA |
| *GAPDH* | FORWARD | ATGGGGAAGGTGAAGGTCG |
| | REVERSE | GGGGTCATTGATGGCAACAATA |

**Supplementary Table 6.** List of primary and secondary antibodies used in the study.

| REAGENT OR RESOURCE | SOURCE | IDENTIFIER | USES |
|---|---|---|---|
| **Antibodies** | | | |
| Rabbit-polyclonal anti-iNOS | Proteintech | 18985-1-AP | WB (1:1000), IF of tissue (1:100), IF of cell (1:300) |
| Rabbit-polyclonal anti-CD206 | Proteintech | 18704-1-AP | WB (1:1000), IF of tissue (1:100), IF of cell (1:300) |
| Mouse-monoclonal anti-IL-6 | Abcam | AB9324 | WB (1:1000), IHC (1:200) |
| Rabbit-monoclonal anti-Arg-1 | Cell Signaling Technology | #93668 | WB (1:1000)， IF of tissue (1:100) |
| Mouse-monoclonal anti-CD68 | Bio-Red | MCA341B | IF of tissue (1:100), IF of cell (1:300) |
| Rabbit-monoclonal anti-JAK1 | Cell Signaling Technology | #50996 | WB (1:1000) |
| Rabbit-monoclonal anti-Phospho-STAT1 | Cell Signaling Technology | #8826 | WB (1:1000), IF of tissue (1:100), IF of cell (1:300) |
| Rabbit- monoclonal anti-STAT1 | Cell Signaling Technology | #14994 | WB (1:1000) |
| Rabbit- polyclonal anti-Col II | Proteintech | 28459-1-AP | IF of tissue (1:100) |
| Rabbit- polyclonal anti-Aggrecan | Proteintech | 13880-1-AP | IF of tissue (1:100) |
| Rabbit-monoclonal anti-Tenascin-C | Abcam | AB108930 | IF of tissue (1:100) |
| Rabbit-polyclonal anti-Fibromodulin | Proteintech | 13281-1-AP | IF of tissue (1:100) |
| Rabbit- polyclonal anti-Osteocalcin | Proteintech | 23418-1-AP | WB (1:1000) |
| Rabbit-Polyclonal anti-Osterix | Invitrogen | PA5-40509 | WB (1:1000) |
| Rabbit- monoclonal anti-Phospho-mTOR | Cell Signaling Technology | #5536 | WB (1:1000), IF of tissue (1:100) |
| Rabbit-monoclonal anti-mTOR | Cell Signaling Technology | #2983 | WB (1:1000) |
| Rabbit-polyclonal anti-Tenomodulin | Abcam | AB203676 | IF (1:100) |
| Mouse-monoclonal anti-TNF-α | Abcam | AB1793 | IHC (1:100) |
| Mouse anti-ACTIN | ZSGB-BIO | TA-09 | WB (1:3000) |
| Rabbit-polyclonal anti-Beta TUBULIN | Proteintech | 10068-1-AP | WB (1:3000) |
| Mouse-monoclonal anti-VINCULIN | Proteintech | 66305-1-lg | WB (1:3000) |
| Rabbit-monoclonal anti-GAPDH | Cell Signaling Technology | #5174 | WB (1:3000) |
| HRP-linked anti-mouse IgG | ZSGB-BIO | ZB-2301 | WB (1:5000) |
| HRP-linked anti-rabbit IgG | ZSGB-BIO | ZB-2305 | WB (1:5000) |
| FITC-labeled goat anti-mouse IgG (H + L) | ZSGB-BIO | ZF-0312 | IF (1:300) |
| FITC-labeled goat anti-rabbit IgG (H + L) | ZSGB-BIO | ZF-0311 | IF (1:300) |
| Rhodamine labeled goat anti-mouse IgG (H + L) | ZSGB-BIO | ZF-0313 | IF (1:300) |
| Rhodamine labeled goat anti-rabbit IgG (H + L) | ZSGB-BIO | ZF-0316 | IF (1:300) |
| Horseradish enzyme labelled goat anti-rabbit IgG | ZSGB-BIO | PV9001 | IHC |
| Horseradish enzyme labelled goat anti-mouse IgG | ZSGB-BIO | PV9002 | IHC |

IF: Immunofluorescence; WB: Western blotting; IHC: Immunohistochemistry

**Supplementary Table 7.** Software.

| Software | |
|---|---|
| ChemDraw 20.0 | https://www.chemdraw.com. |
| Image J (v1.53k) | https://imagej.nih.gov |
| Graph Pad Prism 9.00 | https://www.graphpad.com |
| Micro-CT Evaluation CTAnsoftware (version 1.15) | http://www.blue-scientific.com/bruker-micro-ct-software |
| NRecon | http://www.blue-scientific.com/bruker-micro-ct-software |
| CTvox | http://www.blue-scientific.com/bruker-micro-ct-software |
| OMNI Specta | https://www.thermofisher.cn |
| LAS X 3.0 | https://www.leica-microsystems.com.cn |
| Origin2021 | https://www.originlab.com/ |
| NIS-Elements | https://www.nis-elements.com |
| ZEN 2.3 | https://www.zeiss.com.cn |