**Supplemental Figure Legends**

Supplemental Figure 1. Characterization of EVs isolated from human adipose-derived MSCs. (A) Morphology of the isolated EVs as imaged by transmission electron microscopy (scale bar: 100 nm). (B) Size distribution of isolated EVs as determined by dynamic light scattering. (C) Representative Western blots for the detection of the markers in isolated EVs and whole lysates of MSCs.

Supplemental Figure 2. MSC-EVs suppressed LPS-induced inflammatory response in vitro. BMDMs were cultured alone, with LPS (100 ng/mL), or with MSC-EVs (100 µg/ml) plus LPS (100 ng/mL) for 24 h. Then, BMDMs were harvested for qRT-PCR analysis to determine mRNA expression for IL-1β and TNF-α. Culture of BMDMs with MSC-EVs resulted in suppressed proinflammatory mRNA levels (IL-1β and TNF-α) in response to LPS. One-way analysis of variance (ANOVA) with Bonferroni’s post hoc analysis was used for analysis. Data are presented as mean ± SD; n = 8. \*\**p* < 0.01 and \*\*\**p* < 0.001.

Supplemental Figure 3. Effect of lower dose of MSC-EVs on lung permeability and cell infiltration. Mice were divided into the following 4 groups: control, LPS, LPS + EVs IV (25 µg), and LPS + EVs IT (25 µg). Both EVs IV and IT at 25 µg did not reduce protein concentration, total cell counts, and neutrophil counts in the BAL harvested at 48 h after LPS insult. Kruskal-Wallis test with Dunn’s post hoc test was used for the analysis. Data are expressed as mean ± SD; *n* = 6. \*\*\* *p* < 0.001.

Supplemental Figure 4. Both IV and IT administration of MSC-EVs alleviate LPS-induced inflammatory response and affect macrophage polarization. Mice were divided into the following 5 groups: control, LPS, LPS + MSCs IV (1 × 106 MSCs), LPS + EVs IV (50 µg), and LPS + EVs IT (50 µg). (A) BAL cytokine (IL-1β, IL-6 and TNF-α) levels were determined via a multiplex cytokine array at 48 h after LPS insult. (B) iNOS, ARG-1, and IL-10 mRNA levels in the BAL alveolar macrophages at 48 h after LPS insult were examined via qRT-PCR. One-way ANOVA with Bonferroni’s post hoc test was used for the analysis. Data are expressed as mean ± SD; *n* = 8-9. \**p* < 0.05; \*\**p* < 0.01; and \*\*\* *p* < 0.001.

Supplemental Figure 5. miR-27a-3p knockdown (anti-miR-27a-3p) in mice abolishes the therapeutic effect of MSC-EVs. Mice were inoculated intratracheally with lenti-anti-miR-27a-3p expressing GFP or anti-miR control 5 days before intratracheal instillation of LPS. (A) BAL macrophages were examined for GFP positive cells via fluorescent microscopy 5 days later. (B) Thirty minutes after LPS IT treatment, mice were treated with EVs IT (50 µg). BAL was harvested at 48 h after LPS treatment. miR-27a-3p knockdown in vivo increased protein concentrations, total cell counts, and neutrophil counts in the BAL. (C) Total cells in the BAL were harvested at 48 h after LPS treatment. Cells were then stained with PE-conjugated anti-mouse F4/80 antibody and APC anti-mouse CD206 antibody for phenotypical analysis via flow cytometry. Data are expressed as percentage of CD206+ cells in total F4/80+ macrophages. (D) Expression of markers for M1 (iNOS and IL-1β) and M2 (ARG-1) in BAL macrophages was assayed by qRT-PCR. Mann-Whitney test was used for analysis. Data are presented as mean ± SD; n = 6-7. \**p* < 0.05.

Supplemental Figure 6. NFKB1 is a target gene of miR-27a-3p. (A) Sequence alignments among mouse miR-27a-3p, NFKB1 3’UTR, and mutant NFKB1 3’UTR were highlighted. (B) pGL3-NFKB1 3’UTR (WT 3’UTR) or mutant pGL3-NFKB1 3’UTR (mutant 3’UTR) was co-transfected with pcDNA-miR-27a-3p (miR-27a-3p) or empty pcDNA vector (Con) into HEK293 cells. Relative luciferase activities were determined 48 h after transfection. Kruskal-Wallis test with Dunn’s post hoc test was used for the analysis. Data are presented as mean ± SD; n = 3. \**p* < 0.05. ns = not statistically significant.