# Supplementary Information

## Local transplantation of GMSC-derived exosomes promotes vascularized diabetic wound healing by regulating Wnt/β-catenin pathways

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# Supplementary Materials and Methods

### Internalization of exosomes by HUVECs under high glucose condition

Using DIO-labeled GMSCs, the cell culture supernatant was collected, and DIO-labeled exosomes were extracted by ultracentrifugation, the steps were the same as before. DIO-labeled exosomes emitted green fluorescence and were co-cultured with blue-labeled HUVECs (Procell) in high glucose (HG) medium (contains 35.5mM glucose) for 24 h, then were observed under the confocal microscope (Figure S2).

### Preparation and Characterization of PHE

First, nHAP were generated by high-gravity method and PLGA/nHAP microsphere were prepared by emulsion-solvent evaporation method according to previous works[27]. Subsequently, we

dispersed the microspheres in 40 ml of 0.2 mol/L NaOH solution and got hydrolyzed PLGA/nHAP porous microspheres. Then, EPL were added into the buffer containing the hydrolyzed PLGA/nHAP porous microspheres. Finally, after washed by 1 mol/L NaCl solution for three times and washed by water for another five times, PHE porous microspheres were freeze-dried.

Scanning electron microscope (SEM) was used to observe the internal morphology of the microsphere (Figure S2A), and the types of surface elements can be determined by element mapping (Figure S2B). In addition, antibacterial experiments are used to prove that PHE has good antibacterial ability (Figure S3).

**GMSCs-Exo combined with PHE accelerated wound repair in diabetic mice model**

Fifty 8-week-old male db/db mice (SPF, 40-50g) were purchased from SPF (Beijing) Biotechnology Co., Ltd, and raised in the Animal Laboratory of Chinese PLA general hospital. After 2 weeks adaptive feeding, all the animals were given high-fat and high-sugar feed for another 2 weeks. Weight and blood glucose were recorded every three days. The day before the experiment, the mice were fasted for 12 hours, and the preoperative body weight and fasting blood glucose were measured and recorded. Mice with fasting blood glucose >16.7 mmol/L were selected into the experimental group. Then, 2 mice were randomly selected to be sacrificed, and the pancreatic tissue was excised to serve as the experimental group of the pancreatic tissue structure of diabetic mice (Figure S4).

In addition, the thickness of neo-epithelium was also observed by H&E staining after 2 weeks. The neo-epithelial layer of PHE@Exo was significantly thicker than the other three groups, while Exo and PHE also had a thicker neo-epithelial layer than control (Figure S5A). Masson Trichrome staining demonstrated that more extensive collagen deposition was seen in PHE@Exo, and the defect sites in PHE@Exo were almost covered by neo-epithelium with more mature and wavy collagen fibers after 2 weeks. Exo and PHE also showed thicker and better arranged collagen than control (Figure S5B).

## Supplementary Figures

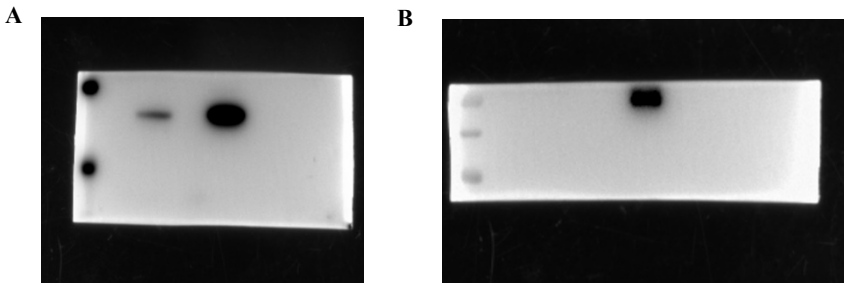


**Figure S1:** Raw data of western blot of proteins expression of Exo**. A.** CD63. **B.** Tsg101.

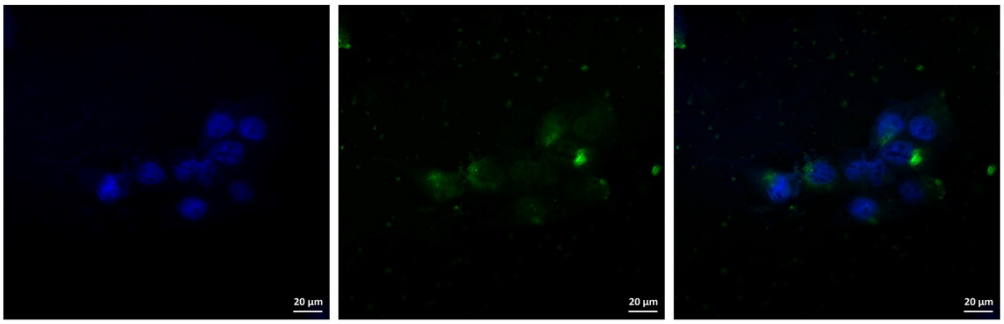


**Figure S2:** Abundant green-fluorescent (GMSCs-Exo) appeared around blue-labeled nucleus of HUVECs, indicated that exosomes are internalized by blue-labeled HUVECs under high glucose condition.

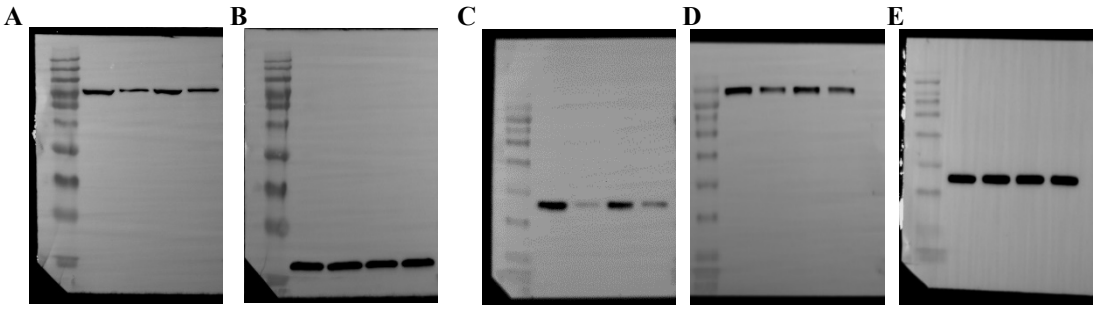


**Figure S3:** Raw data of western blot of proteins expression of Wnt/β-catenin**. A.** β-catenin. **B.** Histone H3. **C.** Cyclin D3. **D.** N-cadherin. **E.** GADPH**.**

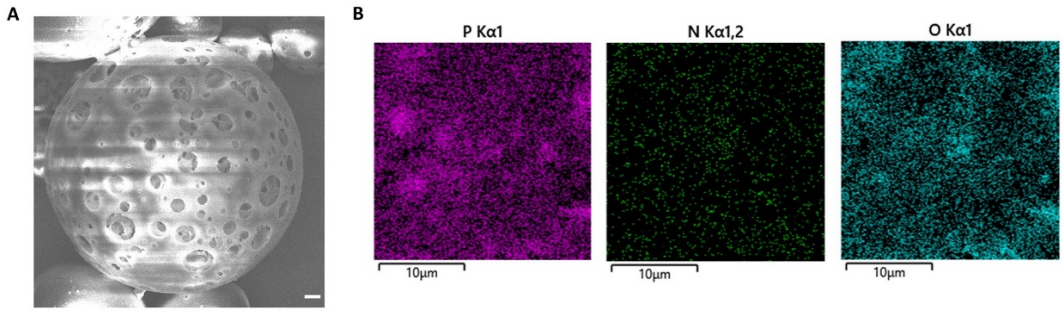


**Figure S4:** SEM and mapping of PHE. **A.** PHE showed porous microsphere structure under SEM. Scale bar: 1μm. **B.** P, N, and O elements can be detected on the surface of PHE porous microspheres, indicating that nHAP and EPL are successfully combined with PLGA.

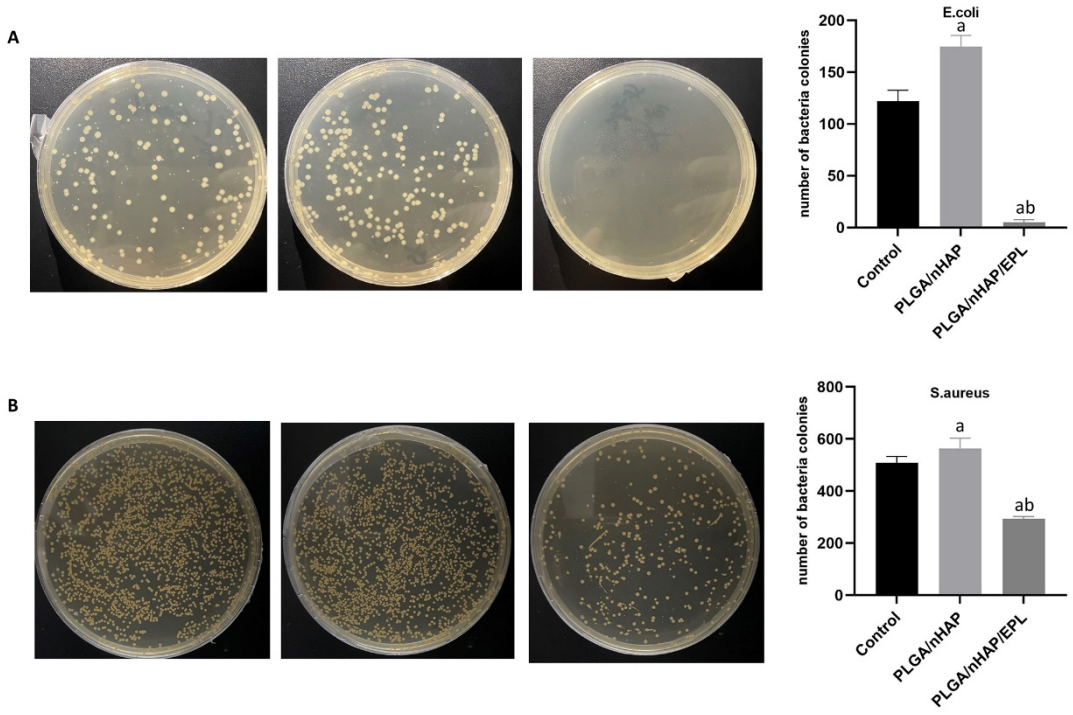


**Figure S5:** The antibacterial experiment presented the antibacterial ability of PHE. **A.** Significant antibacterial effect of PHE on Escherichia coli. **B.** Significant antibacterial effect of PHE on Staphylococcus aureus.

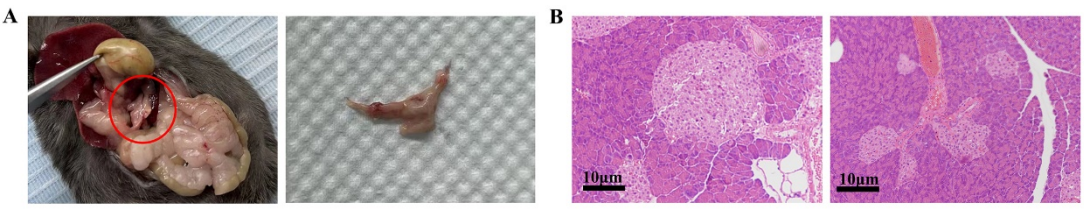


**Figure S6: A.** The anatomic position and appearance of pancreas. **B.** H&E staining of the pancreatic tissue in normal (left) and diabetic mice (right).

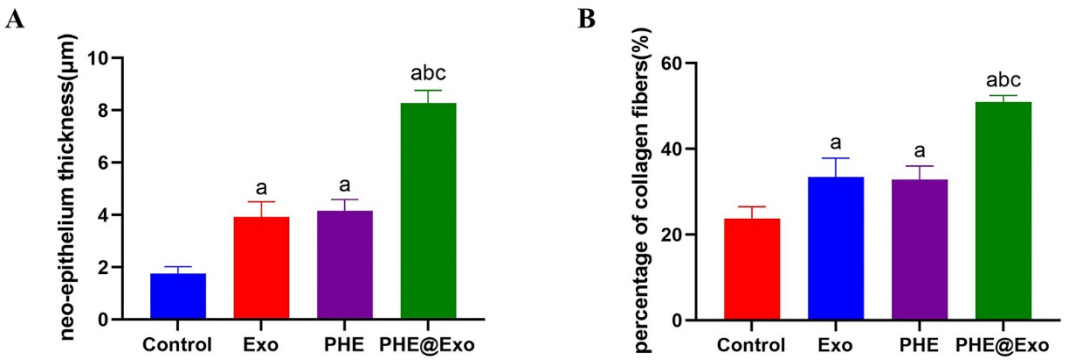


**Figure S7: A.** Quantitative analysis of neo-epithelium thickness by H&E staining after 2 weeks. **B.** Quantitative analysis of the percentage of collagen by Masson's trichrome staining in each group after 2 weeks.