## Supplementary Table 1 Application of exosomes secreted by other origins-derived stem cells in diabetic full-thickness acute cutaneous wounds model

<table>
<thead>
<tr>
<th>Study No.</th>
<th>Institution (Nation)</th>
<th>Exosomes source</th>
<th>Intervention, administration, dose and time</th>
<th>Control Model species</th>
<th>Wound diameter (cm × cm)</th>
<th>Therapeutic effect</th>
<th>Molecular mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Wang et al. (2021)</td>
<td>Human adipose tissue</td>
<td>1. HypADSC-Exos; injected subcutaneously into four mid-points of the wound edge; 2 mg in 100 μL PBS; at Day 0</td>
<td>Untreated Nude mice (BALB/c)</td>
<td>0.8 cm × 0.8 cm (square)</td>
<td>1. Accelerated skin wound healing. 2. Complete re-epithelialization and cuticle covering on the epidermis. 3. Upregulated expression of PI3K/AKT pathway (CD31, TGF-β) and growth factors (CD31, TGF-β, pathway PDGF, VEGF and PDGF); downregulated inflammatory factor (IL-6). 4. Improved angiogenesis (CD31, VEGF)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Shiek et al. (2020)</td>
<td>Rat adipose tissue</td>
<td>1. ADSC-Exos + PUAO-CPO scaffolds; applied on the wound beds; 100 μg/scaffold; at Day 0</td>
<td>Untreated Rats (wister)</td>
<td>8 mm × 2</td>
<td>1. Accelerated wound closure. 2. Enhanced granulation tissue, epithelial, hair follicles and sebaceous glands formation, re-</td>
<td></td>
</tr>
</tbody>
</table>
2. ADSC-Exos + PUAO scaffolds; applied on the wound beds; 100 μg/scaffold; at Day 0
3. PUAO-CPO scaffolds; applied on the wound beds; 100 μg/scaffold; at Day 0
4. PUAO scaffolds; applied on the wound beds; 100 μg/scaffold; at Day 0

3. Increased fibroblast proliferation, collagen deposition (Col I, Col III) and remodeling (Col I remodeling).
4. Attenuated oxidative stress and increased angiogenesis.
5. Enhanced wound healing in S. aureus and P. aeruginosa infected diabetic wound ulcers.

1. Nrf2 overexpressed ADSC-Exos + EPCs; injected; dose not mentioned; at Day 0
2. ADSC-Exos + EPCs; injected; dose not mentioned; at Day 0
3. EPCs; injected;

1. Accelerated cutaneous wound healing.
2. Increased granulation tissue formation, angiogenesis, collagen deposition and the expression of growth factor.
3. Reduced levels of inflammation and oxidative stress (ROS)-related proteins.
<table>
<thead>
<tr>
<th>Study</th>
<th>ADSC-Exos Application</th>
<th>Control Treatment</th>
<th>Treatment Duration</th>
<th>Animals</th>
<th>Results</th>
</tr>
</thead>
</table>
| Wang et al. (2020)     | ADSC-Exos; injected into the dermis at the edge of the wound in 6 directions; 0.2 mL; at Day 0 | PBS (0.2 mL)      | Mice              | BALB/c 8 mm c | 1. Accelerated cutaneous wound healing.  
2. Increased re-epithelization.  
3. Promoted collagen synthesis and deposition (extensive deposited and neatly arranged collagen fibers).  
4. Enhanced angiogenesis (CD31, number of microvessels). |
| The Second Affiliated Hospital of Nanchang University (China) | | | | | |

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<th>Study</th>
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<th>Control Treatment</th>
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<th>Animals</th>
<th>Results</th>
</tr>
</thead>
</table>
| Lv et al. (2020)       | miR-21-5p overexpressed ADSC-Exos; applied to the wound bed; 200 μL; at Day 0, every 3 days | Untreated (Sprague-Dawley) | Rats              | Sprague-Dawley 15 mm | 1. Accelerated cutaneous wound healing.  
2. Promoted collagen deposition, and tissue matrix remodeling.  
3. Promoted re-epithelialization.  
4. Controlled inflammation (limited inflammatory cells infiltrated).  
5. Promoted angiogenesis and vascular maturation (CD31, α-SMA). |
| The Third Affiliated Hospital of Sun Yat-sen University (China) | | | | | |
applied to the wound bed; 200 μL; at Day 0, every 3 days
4. miR-21-5p; applied to the wound bed; 200 μL; at Day 0, every 3 days

**Jiang et al. (2022)**[6]

1. **ADSC-Exos** + matrix metalloproteinase degradable polyethylene glycol (MMP-PEG) hydrogel; dressed on the wound; dose not mentioned; at Day 0

2. **MMP-PEG** hydrogel; dressed on the wound; at Day 0

1. Accelerated cutaneous wound healing.
2. Promoted re-epithelialization and collagen deposition.
3. Regrew cutaneous appendages.
4. Promoted cell mitosis (Ki67) and proliferation (PCNA) in diabetic wounds.
5. Enhanced angiogenesis (CD31, α-SMA).
6. Improved phosphorylation of AKT.
1. ADSC-Exos; topically treated; 200 µg in 200 µL PBS; at day 1, 4, 7, 10, 13 and 16

1. Accelerated cutaneous wound healing.
2. Enhanced wound contraction and re-epithelialization.
3. Promoted granulation tissue formation and collagen deposition.
4. Increased proliferation (Ki67) of basal keratinocytes and dermal fibroblasts.
5. Promoted angiogenesis (CD31, α-SMA, VEGF).
6. Upregulated expression of stromal cell-derived factor (SDF)-1, keratinocyte growth factor (KGF).
7. Upregulated protein expression related to ECM remodeling (Col-I, α-SMA, Smad3 and TGF-β).

1. linc00511 overexpressed ADSC-Exos + EPCs; injected; dose not mentioned; PBS Rats (Sprague-Dawley) Not mentioned

1. Accelerated cutaneous wound healing.
2. Alleviated cutaneous tissue damages.
of Central South University (China)

1. circ-Snhg11 overexpressed ADSC-Exos; injected subcutaneously at 4 sites around the wound; 200 μg in 100 μL PBS, 25 μL/site; at Day 0

2. Hypoxia-pretreated ADSC-Exos; injected subcutaneously at 4 sites around the wound; 200 μg in 100 μL PBS, 25 μL/site; at Day 0

3. Enhanced collagen deposition. BTRC-mediated Twist1 protein degradation.
4. Promoted angiogenesis (CD31, VEGF) via inhibiting Twist1 via inhibiting Twist1 protein degradation.
5. Suppressed inflammatory factors (IL-6, IL-1β, TNF-α).
6. Inhibited expression of PAQR3 and upregulated Twist1.

Shi et al. (2022) [9]

Affiliated Hospital of Adipose tissue
Nantong University (China)

1. Accelerated cutaneous wound healing (more effective). circ-Snhg11/miR-144–3p/HIF-1α/VEGF signaling pathway;
2. Decreased expression of inflammatory factors (IL-6, IL-1β, TNF-α).
3. Promoted angiogenesis (CD34, VEGF).
4. Induced macrophage polarization from M1 (iNOS) to M2 (CD206) phenotype.
5. Increased STAT3 and VEGF expression.
1. Hypoxia-pretreated ADSC-Exos; injected subcutaneously at 4 sites around the wound; 200 μg in 100 μL PBS, 25 μL/site; at Day 0

2. ADSC-Exos; injected subcutaneously at 4 sites around the wound; 200 μg in 100 μL PBS, 25 μL/site; at Day 0

3. mmu_circ_0001052-modified ADSC-Exos; injected subcutaneously at 4 sites around the wound; 200 μg in 100 μL PBS, 25 μL/site; at Day 0

4. ADSC-Exos + vector; injected subcutaneously at 4 sites around the wound; 200 μg in 100 μL PBS, 25 μL/site; at Day 0

5. mmu_circ_0001052-modified ADSC-Exos; injected subcutaneously at 4 sites around the wound; 200 μg in 100 μL PBS, 25 μL/site; at Day 0

1. Accelerated cutaneous wound healing.
2. Decreased expression of inflammatory factors (IL-6, IL-1β, TNF-α).
3. Promoted angiogenesis (CD34).
4. Induced macrophage polarization from M1 (iNOS) to M2 (CD206) phenotype.
5. Upregulated expression of circ-Snhg11.

1. Accelerated cutaneous wound healing.
2. Promoted angiogenesis (CD31).
3. Diminished inflammatory cells.
4. Promoted granulation tissue formation.

<table>
<thead>
<tr>
<th>iPS-Exos;</th>
<th>Mice</th>
<th>PBS (20 μl)</th>
<th>8 mm × 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>injected subcutaneously; 4 μg in 20 μl PBS; at Day 0</td>
<td>C57BLK S/J-Leprdb (db/db)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Accelerated cutaneous wound healing.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Promoted re-epithelialization.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Enhanced angiogenesis (CD31, α-SMA, vessel density).</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>4. Promoted regeneration of peripheral nerve fibers (nerve density).</td>
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<td></td>
</tr>
</tbody>
</table>

### Chen et al. (2018) [12]

<table>
<thead>
<tr>
<th>Con shRNA-transfected USC-Exos; injected subcutaneously around the wounds at 4 sites (25 μL per site); 200 μg in 100 μL PBS; at Day 0</th>
<th>Mice</th>
<th>PBS (100 μL)</th>
<th>6 mm × 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Accelerated cutaneous wound healing.</td>
<td>C57BL6/6</td>
<td></td>
<td></td>
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<tr>
<td>2. Promoted re-epithelialization DMBT1/VEGFA pathway; and dermis with hair follicles and fat cells).</td>
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<tr>
<td>3. Reduced scar formation.</td>
<td>PI3K/AKT pathway.</td>
<td></td>
<td></td>
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<tr>
<td>4. Promoted collagen deposition (larger amounts of wavy collagen fibers).</td>
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<td></td>
<td></td>
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<tr>
<td>5. Enhanced proliferation of skin</td>
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</tr>
</tbody>
</table>
1. Epidermal stem cell-derived exosomes (ESC-Exos); injected subcutaneous around the wound at 4 sites (40 μl per site) + at the wound center (40 μl); 50 μg/ml in total 200 μl PBS; at Day 0
2. Epidermal stem cells (ESCs); injected subcutaneous around the wound at 4 sites (40 μl per site) + at the wound center (40 μl); 5 × 10^6/ml in total 200 μl PBS; at Day 0
3. Fibroblast-derived exosomes (FB-Exos); injected subcutaneous around the wound at 4 sites (40 μl per site) + at the wound center (40 μl); dose not mentioned; at Day 0
4. Promoted wound cell proliferation (Ki67).
5. Enhanced angiogenesis (CD31, vessel density).
7. Promoted macrophages polarization from M1 (iNOS, CD11b) to M2 (YM1, CD206, TGFB, CD206).

Wang et al. (2022)[13]
Beth Israel Deaconess Medical Center of Harvard Medical School (USA)

Mice 6 mm × 2 Mice (db/db) 2 PBS (200 μl)
<table>
<thead>
<tr>
<th>Ren et al. (2022)</th>
<th>Union Hospital, Tongji Medical College, Huazhong University of Science and Technology (China)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. ADSC-Exos + normal mouse IgG; injected subcutaneous around the wound at 5 sites; 50 μg ADSC-Exos; at Day 0</td>
<td>Mice (C57BL/6)</td>
</tr>
<tr>
<td>2. ADSC-Exos + normal mouse IgG; injected subcutaneous around the wound at 5 sites; 50 μg ADSC-Exos; at Day 0</td>
<td>PBS</td>
</tr>
<tr>
<td>3. ADSC-Exos + anti-HSP90 antibody; injected subcutaneous around the wound at 5 sites; 50 μg ADSC-Exos; at Day 0</td>
<td></td>
</tr>
</tbody>
</table>

Increased expression of CD31, PLGF-2, VEGF-A, and TGF-β3, prolactin, MMP-3, and TGF-β2.

1. Accelerated cutaneous wound healing (anti-HSP90 antibody could completely inhibit this effect).

2. Promoted collagen deposition (more extensive and better-organized).

3. Alleviate oxidative stress (promoted ROS scavenging, reduced apoptotic cells).

4. Enhanced angiogenesis (CD31, α-SMA).

5. Promoted cell proliferation in granulation tissue (Ki67, PCNA).
References


10 Liang ZH, Pan NF, Lin SS, Qiu ZY, Liang P, Wang J, Zhang Z, Pan YC. Exosomes from mmu_circ_0001052-modified adipose-derived stem cells promote angiogenesis of DFU via miR-


