**Trace Element-Dictated Exosome Modules and Self-Adaptive Dual-Network Hydrogel Orchestrate Diabetic Foot Regeneration through Complement-Mitochondria-Autophagy Circuitry**

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**Background and aims.** Diabetic foot ulcers (DFU), trapped in the "inflammation-ischemia" vicious cycle, present significant clinical challenges. This study proposes a coordinated therapeutic strategy integrating "Trace element (TE) programming-Exosome (Exo) engineering-Intelligent delivery" to overcome functional and delivery limitations of Exo.

**Methods.** This system is based on a double-network structure constructed from oxidized hyaluronic acid (OHA) and lipoic acid-modified chitosan (LACS). A Schiff base reaction rapidly forms an injectable precursor gel, which is then subjected to UV-assisted secondary crosslinking to significantly enhance its mechanical properties and stability.

**Results.** Through Fe-Mg-Zn-Mn-Se multi-TE synergy and 3D dynamic culture, we constructed high-activity engineered Exo (3D-TE-Exo) with a yield of 1.9×1012 particles/mL, representing a 29-fold increase over conventional culture. 3D-TE-Exo mitigates inflammation and promotes angiogenesis through a triple mechanism involving C1QBP-mediated regulation of the complement pathway, restoration of mitochondrial membrane potential, and remodeling of autophagic flux, thereby disrupting the pathological cycle. Furthermore, a dual-network hydrogel featuring dynamic Schiff base bonds and UV-triggered disulfide bond reorganization enables precise Exo release and prolonged retention. Remarkably, 89.71% wound closure was achieved in DFU rats at Day 14 versus 50.64% in controls.

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**Figure 1.** The exosomes (3D-TE-Exo) with high activity were constructed by Fe-Mg-Zn-Mn-Se multi-TE synergy and 3D dynamic culture.

**Conclusion/Discussion.** This work establishes a novel paradigm for synergistic design of engineered Exo and smart biomaterials, demonstrating clinical translation potential and pioneering multi-target intervention approach for DFU therapy.

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(1) Wang S, et al. Adv Sci. 2023;10:e2303167.

(2) Wang S, et al. J Control Release. 2024;369:420–43.