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•Review•

Advances in the combination of stem cell exosomes with medical devices-the new direction for combination products

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[ABSTRACT] Exosomes (exos), nanoscale extracellular vesicles, play a critical role in tissue development and function. Stem cell-derived exos, containing various tissue repair components, show promise as natural therapeutic agents in disease treatment and regenerative medicine. However, challenges persist in their application, particularly in targeted delivery and controlled release, which are crucial for enhancing their biological efficacy. The integration of medical devices may provide a superior platform for improving drug bioavailability. Consequently, the combination products of stem cell-derived exos and medical devices present novel opportunities for expanding the therapeutic potential of exosomes. This review offers a comprehensive overview of the current research frontier in stem cell-derived exos combined with medical devices and discusses the prospective challenges and future prospects in this field.

[KEY WORDS] Stem cell exosomes; Medical devices; Tissue repair; Combination products
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Introduction

Exosomes (exos), nanoscale vesicles secreted by cells, function as messengers that regulate the development of surrounding tissues [1-3]. Among these, stem cell-derived exos, such as mesenchymal stem cell-derived exos (MSC-exos), carry diverse therapeutic substances, continuously exhibiting efficacy in reversing aging, facilitating tissue repair, and promoting regeneration in various forms [4, 5], thus holding considerable potential as natural therapeutic agents for treating various diseases. Moreover, given their ideal biocompatibility and availability, they possess immense clinical application prospects [6]. However, there is an urgent need to develop novel drug delivery methods to incubate exos with high retention rates and precise implantation characteristics tailored to specific disease features [7, 8].

Medical devices play a crucial role in clinical therapy by contributing to the diagnosis, prevention, and treatment of diseases, as well as providing physiological support [9, 10]. Novel medical device materials, such as tissue engineering scaffolds and surgical dressings, have the potential to address multiple diseases [11]. However, challenges persist in optimizing these materials, particularly in addressing rejection reactions and material degradation within the body [12].

The integration of pharmaceuticals with medical devices to create a category of combination products that merge the functionalities of both may be crucial for enhancing the bioavailability of stem cell-derived exos and improving the biocompatibility of medical devices [13, 14]. Medical devices not only confer exos with properties such as controlled release, precise implantation, and sustained retention but also provide synergistic effects to promote tissue repair due to their inherent composition [15]. Concurrently, the incorporation of stem cell-derived exos could provide autologous components for medical devices, potentially mitigating immune rejection during use [16]. Consequently, investigating diverse forms of drug delivery for stem cell-derived exos in conjunction with medical devices, elucidating their compatibility mechanisms, and broadening their application scope represent significant developmental directions in the field of stem cell-derived exo therapy.

This review comprehensively examines the cutting-edge research on stem cell-derived exos combined with medical devices. It elucidates the synergistic mechanisms by which these combinations enhance therapeutic outcomes for various diseases. Additionally, the review addresses potential challenges in developing this drug-device combination product and provides insights into future research directions (Scheme 1). Ultimately, this review presents a strategic perspective on integrating stem cell-derived exos with medical devices, offering valuable guidance for future developments

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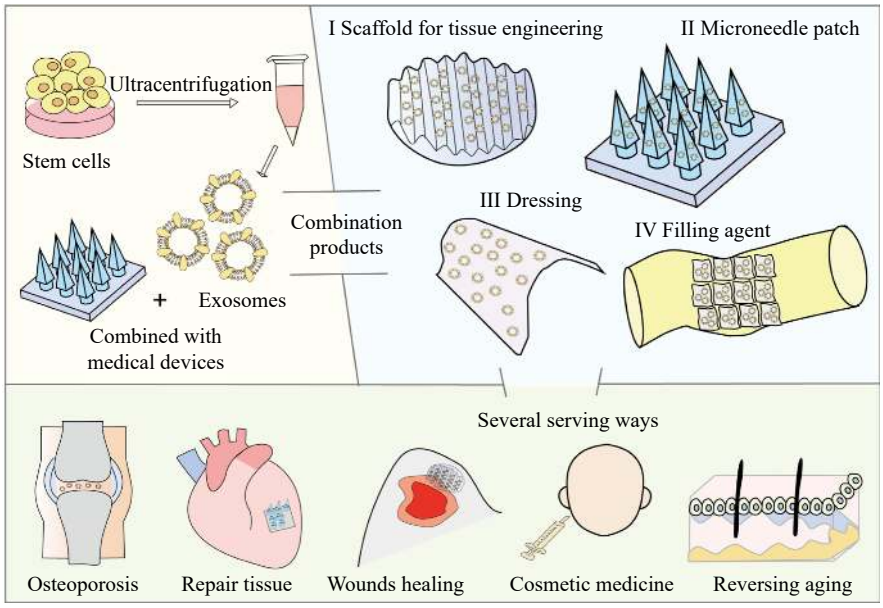


Scheme 1 Combination products and applications produced by exos with medical devices.

in this field.

Exos and Tissue Engineering Scaffold Materials

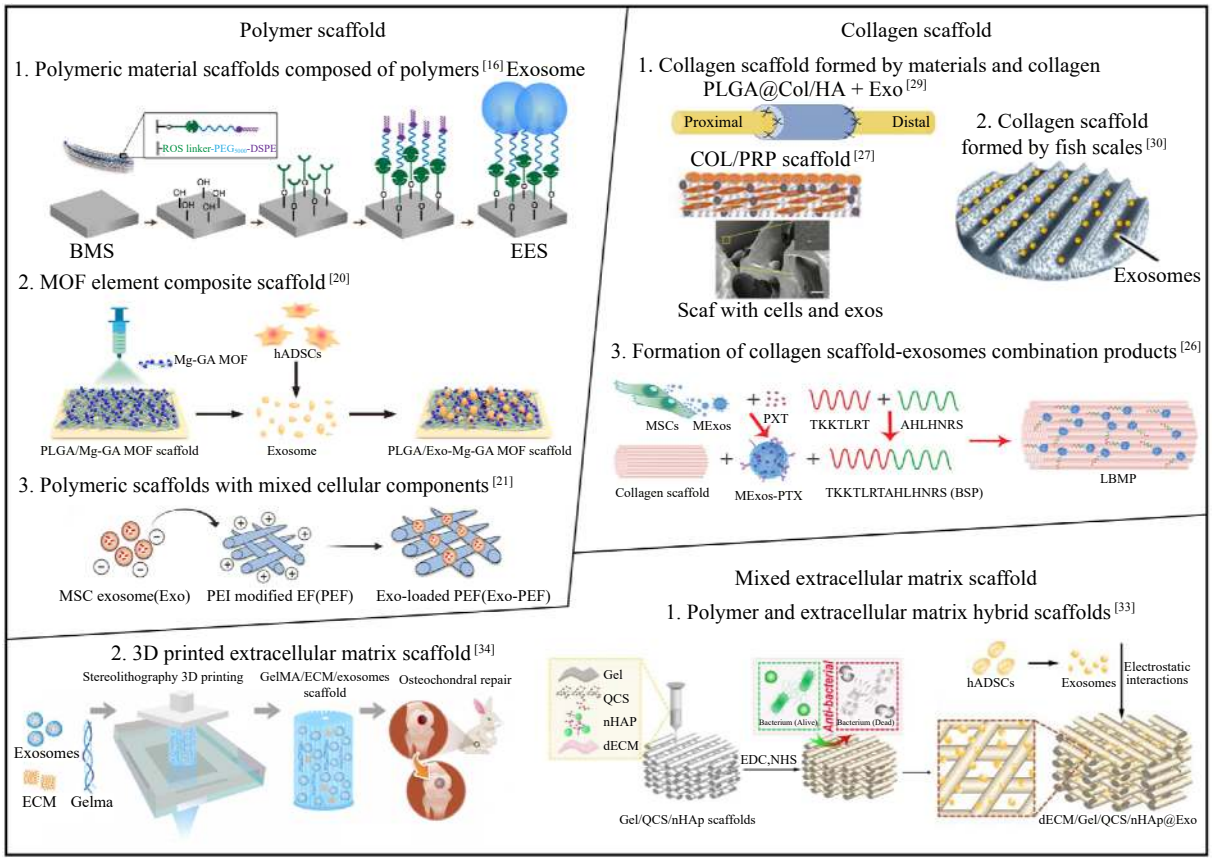
Tissue engineering scaffolds, encompassing polymeric scaffolds, collagen-based scaffold materials, and decellularized matrices, function as certified medical devices extensively utilized in numerous clinical trials for bone repair, neural maintenance, wound healing, and other applications [17-18]. These scaffolds provide a stable framework for the loading and release of exos, offering an optimized solution for treating diseases that require precise colonization, long-term storage, and a consistent supply of exos. Consequently, integrating stem cell-derived exos with scaffold materials into combination products enhances the bioavailability of both components, facilitating multi-level and multi-angle synergistic therapy (Scheme 2). Table 1 presents detailed information about these combination products.

Polymer scaffolds

Polymeric scaffold materials, encompassing inorganic polymer scaffolds, polymer-hydrogel hybrid scaffolds, and polymer-metal organic framework (MOF) based hybrid scaffolds, represent one of the earliest developed and certified medical devices in the field of tissue engineering scaffolds [19]. While significant advancements have been made in the production technologies, architectural designs, and evaluation methods of these polymeric scaffolds, optimizing their biocompatibility within the body remains a crucial area for improvement. The application of stem cell-derived exos as coatings on these scaffold materials serves to camouflage the scaffolds as "autologous components", thereby mitigating *in vivo* rejection reactions and facilitating the delivery of repair components into the pathological environment while providing necessary tissue support.

The integration of a composite scaffold enhances the precise engraftment and stable retention of stem cell-derived exos at the injury site while providing a three-dimensional environment for tissue repair, thereby amplifying the efficacy of exo function. These combination products demonstrate significant therapeutic effects in wound healing and three-dimensional tissue regeneration. Hu *et al.* [16] coated metal scaffold materials with MSC-exos, effectively "disguising" the scaffold to evade smooth muscle cells and the body's immune system, promoting endothelial cell migration at the damaged site and accelerating vascular healing and ischemic repair. In a similar vein, Kang *et al.* [20] applied exos from human adipose stem cells onto functionalized acellular poly (lactic-co-glycolic acid)-metal organic framework (PLGA-MOF) hybrid scaffolds, demonstrating efficient osteogenic, angiogenic, and anti-inflammatory effects. Su *et al.* [21] incorporated mesenchymal stromal cell-derived exos into fibrous polyester scaffold materials, which acted as recruiters and trainers of immune cells, respectively, to synergistically promote beneficial macrophage and regulatory T cell responses in mouse skin wounds, facilitating wound healing. It is anticipated that composite products based on polymer scaffolds with incorporated exos will enhance the inherent biocompatibility of the material. These products have potential applications in various tissue defect diseases that require both exo-activated remodeling processes and three-dimensional structural support for tissue remodeling.

The integration of absorbable tissue engineering scaffolds with stem cell-derived exos presents an effective approach for enhancing osteogenesis. Liu *et al.* [22] identified high-quality osteogenic exos (BMSC-OI-exos) from MSC-exos, which, when carried by mesoporous bioactive glass (MBG) scaffolds, rapidly filled rat cranial defects, offering a promising strategy for bone repair. Similarly, exos derived from human dental pulp stem cells (hDPSCs-exos) were in-



Scheme 2 Combination products of stem cell-derived exos with tissue engineering scaffold materials.

corporated into three-dimensional tissue-engineered scaffolds composed of PLGA and polyethylene glycol (PEG) [23]. This combination product was directly implanted into mouse mandibular defects, circumventing transplantation immunogenicity and achieving extracellular vesicle-mediated bone regeneration in a clinically relevant manner. In these applications, stem cell-derived exos function as initiators of tissue repair processes, while the tissue scaffold provides three-dimensional support for cell adhesion and growth. Compared with the use of exos or tissue engineering scaffolds independently, this combined approach demonstrates enhanced osteogenic activity and improved tissue adaptability repair, thus offering broader applicability.

Collagen scaffold

Collagen-mixed inorganic material scaffolds represent a significant advancement in enhancing the biocompatibility of inorganic materials. Collagen scaffolds, serving as natural organic templates for bone biomineralization, play a pivotal role in promoting bone formation [24]. Furthermore, collagen, being an integral component of cellular structure, is particularly suited as a complementary material to stem cell-derived exos in various applications requiring collagen supplementation. These applications include tissue repair promotion, wound healing, anti-aging interventions, and the synergistic nourishment of aging or damaged tissues [25]. Consequently, the integration of stem cell-derived exos with collagen scaffolds presents a promising approach for cellular component repair.

Primarily, the collagen-protein scaffold provides collagen, synergistically enhancing the efficacy of extracellular vesicles in restoring skin and mucosal integrity. Wang *et al.* [27] developed a composite biomaterial scaffold comprising type I collagen, platelet-rich plasma, and exos derived from adipose-derived stem cells (ADSC-exos). This collagen-based scaffold offered mechanical support and established a conducive environment for keratinocyte growth and migration. In comparison to the individual effects of stem cell-derived exos or collagen-protein scaffold materials, the combined product demonstrated superior promotion of 3D skin tissue remodeling, facilitating the restoration of skin integrity. Furthermore, the combination products of collagen-based scaffolds could potentially address various diseases associated with premature aging. Loading MSC-exos onto hyaluronic acid-enriched collagen scaffolds enhances follicle survival and repairs lesions in prematurely aged ovarian tissues [28], further indicating the unique reparative role of these combination products in reversing damage to various extensible tissues.

The integration of collagen scaffolds and exos demonstrates significant potential for nerve repair applications. Zhang *et al.* [26] developed innovative bio-specific peptides with dual-binding capabilities to type I collagen and exos. The resulting multifunctional collagen scaffold exhibited enhanced mechanical properties and promoted neural stem cell

Table 1 Application forms of stem cell exos and tissue engineering scaffolding materials

Resource of exos	Types of medical devices	Treated disease	Materials for medical devices	Refs
Human bone marrow mesenchymal stem cells	Polymer material scaffold	Promoting revascularization	1,2-bishard acyl-Sn-glycerol-3-phosphate ethanolamine composed polymer material scaffold	[16]
Human adipose mesenchymal stem cells	Polymer material scaffold	Promoting osteogenesis and revascularization	PLGA polymer material scaffold	[20]
Human bone marrow mesenchymal stem cells	Polymer material scaffold	Wound healing	Polyethylenimine and polycaprolactone fibers composed polymer material scaffold	[21]
Human bone marrow mesenchymal stem cells	Polymer material scaffold	Promoting osteogenesis	Multilayer mesoporous bioactive glass scaffolds	[22]
Human dental pulp stem cell	Polymer material scaffold	Promoting osteogenesis	Nanofibrous scaffolds bearing PLGA-PEG-PLGA microspheres	[23]
Human umbilical cord mesenchymal stem cells	Collagen scaffold	Repairing spinal cord	Collagen scaffolds with type I collagen	[26]
Human adipose mesenchymal stem cells	Collagen scaffold	Wound healing	3D collagen scaffold formed with type I collagen and platelet-rich plasma	[27]
Human umbilical cord mesenchymal stem cells	Collagen scaffold	Moisturizing the ovaries	Degradable collagen fiber scaffold	[28]
Human umbilical cord mesenchymal stem cells	Collagen scaffold	Neural remodeling	The composite catheter collagen scaffold was formed by sealing the collagen/hyaluronic acid internal sponge in an electrospun hollow poly (lactic-glycolic acid copolymer) tube	[29]
Human bone marrow mesenchymal stem cells	Collagen scaffold	Promoting osteogenesis	Acellular fish scale scaffolds were obtained by treating fish scales by decellularization and decalcification processes	[30]
Human umbilical cord mesenchymal stem cells	Mixed extracellular matrix scaffold	Promoting osteogenesis	Extracellular matrix derived from cultures of acellular chondrocytes	[32]
Human bone marrow mesenchymal stem cells	Mixed extracellular matrix scaffold	Promoting osteogenesis	Hybrid extracellular matrix scaffolds composed of gelatin, N-trimethyl chitosan, and nano-hydroxyapatite	[33]
Human bone marrow mesenchymal stem cells	Mixed extracellular matrix scaffold	Promoting osteogenesis	3D-printed gelatin-methacrylate cartilage extracellular matrix scaffold	[34]
Human adipose mesenchymal stem cells	Microneedle patch	Reversing aging	Microneedle patch produced by Dongbang Medi-care	[36]
Human umbilical cord mesenchymal stem cells	Microneedle patch	Reversing aging	Microneedle patch produced by Beijing Origife Health Care Co., Ltd., China	[37]
Human adipose mesenchymal stem cells	Microneedle patch	Repairing the scar	Microneedles composed of hyaluronic acid, hydroxypropyl-β-cyclodextrin	[38]
Human umbilical cord mesenchymal stem cells	Microneedle patch	Wound healing	Microneedles composed of porous methacrylate gelatin hydrogels	[39]
Human embryonic mesenchymal stem cells	Microneedle patch	Repairing spinal cord	Microneedles composed of porous gelatin methacryloyl hydrogels	[15]
Rat bone marrow mesenchymal stem cells	Microneedle patch	Repairing spinal cord	Methacryloyl hydrogel microneedles	[40]
Mouse tendon stem cells	Microneedle patch	Healing Achilles tendon	Microneedles composed of methacrylated gelatin and polyvinyl alcohol gels	[41]
Human umbilical cord mesenchymal stem cells	Microneedle patch	Treating cardiac fibrosis	Gelatin microneedles	[42]
Human umbilical cord mesenchymal stem cells	Dressing	Wound healing	Hydrogel dressing prepared by mixing chitosan and silk fibroin	[44]
Rat adipose mesenchymal stem cells	Dressing	Wound healing	Chitosan hydrogel dressing	[45]
Human adipose mesenchymal stem cells	Dressing	Wound healing	The dressing consisting of a mixture of gel and calcium peroxide	[47]
Human adipose mesenchymal stem cells	Dressing	Treating psoriasis	MSCs conditioned medium serving as dressing	[48]
Mouse adipose stem cells	Dressing	Moisturizing the ovaries	Hydrogel dressing in the presence of Ag-S dynamic coordination	[49]

Continued

Resource of exos	Types of medical devices	Treated disease	Materials for medical devices	Refs
Human bone marrow mesenchymal stem cells	Dressing	Promoting osteogenesis	Photoinduced imine cross-linked hydrogel dressing	[50]
Human bone marrow mesenchymal stem cells	Dressing	Neural remodeling	Conductive hydrogel dressings	[51]
Human placental mesenchymal stem cells	Dressing	Repairing spinal cord	Laminin-derived peptide-modified adhesive HA hydrogel dressing	[52]
Human bone marrow mesenchymal stem cells	Filling agent	Promoting osteogenesis	Calcium sulfate-nano-hydroxyapatite nano-bone cement bone-filling agent	[53]
Human adipose mesenchymal stem cells	Filling agent	Promoting osteogenesis	Porous scaffolds with polylactic acid, calcium silicate, and dicalcium phosphate dihydrate mineral doping	[54]
Human dental pulp stem cell	Filling agent	Promoting osteogenesis	Polymers of triblock PLGA-PEG-PLGA and diblock PEG-PLGA were used as a filling agent	[55]
Human adipose mesenchymal stem cells	Filling agent	Wound healing	Hyaluronic acid serving as a filling agent	[56]
Human adipose mesenchymal stem cells	Filling agent	Repairing the scar	The extracellular matrix produced by the MSCs spheroids serving as filling agent	[57]

migration, which is advantageous for recruiting endogenous neural stem cells to spinal cord injury sites, facilitating the repair of complete spinal cord transection. In a similar vein, Tang *et al.* [29] engineered a composite nerve scaffold designed to provide a regenerative environment for Schwann cell proliferation while carrying MSC-exos. This combined product effectively repaired peripheral nerve tissue damage, significantly enhancing synaptic remodeling and nerve regeneration. These findings suggest that such integrated products can serve as effective scaffolds for neural migration, potentially restoring the integrity of neural networks.

Fish scales, primarily composed of collagen and hydroxyapatite, demonstrate significant biodegradability and high toughness, making them excellent sources for collagen-related bone tissue engineering materials [30]. The combination of fish scale-derived bone tissue engineering materials loaded with stem cell-derived exos could enhance the repair capacity of bone tissue damage by facilitating the formation of absorbable bone needles. In this context, Wang *et al.* [30] introduced a novel extracellular vesicle-functionalized decellularized fish scale (DE-FS) scaffold. Exos derived from osteogenic bone marrow mesenchymal stem cells reinforced the tissue support functions of decellularized fish scale scaffolds while permeating bone tissue, promoting bone cell proliferation and regeneration, and improving the efficiency of large-scale bone tissue formation. Furthermore, the raw materials for this combination product are readily accessible, rendering it suitable for large-scale industrial production.

Mixed extracellular matrix (ECM) scaffolds

The ECM, a complex structure comprising collagen, elastin, laminin, and other components, represents one of the most biologically significant scaffold materials. The nutrients within the ECM also contribute to maintaining the activity and performance of exos [31]. Consequently, incorporating stem cell-derived exos into ECM scaffolds may enhance tissue architecture and bioavailability. Jiang *et al.* [32] extracted exos derived from human umbilical cord Wharton's jelly mesenchymal stem cells (hWJMSC-Exos), which possess immunomodulatory and tube-remodeling properties, and incorporated them into acellular cartilage extracellular matrix (ACECM) tissue engineering scaffolds. The resulting combination products demonstrated superior efficacy in synergistically promoting rabbit distal femoral cartilage regeneration and regulating the immune environment.

The utilization of 3D printing technology to produce "bio-ink" from ECM-gelatin bio-scaffolds represents an innovative approach to tissue engineering. Kang *et al.* [33] employed this technology to fabricate a hybrid ECM scaffold composed of decellularized ECM, gelatin, quaternized chitosan, and nanohydroxyapatite, featuring an extensive microchannel network. This hybrid scaffold exhibits favorable printability and stable physical properties, facilitating targeted implantation and long-term preservation of MSC-exos. The combined product significantly enhanced vascularization and osteogenesis, effectively repairing cranial defects. In a similar vein, Chen *et al.* [34] applied this method to osteoarthritis treatment. They developed a 3D-printed "bio-ink" scaffold using cartilage ECM and gelatin methacrylate, incorporating radially oriented channels and BMSC-exos. This composite significantly increased macrophage recruitment within 3−4 days post-implantation, promoting tissue cell regeneration and fibrous remodeling through enhanced immune response.

In summary, ECM scaffolds possess a structure and composition analogous to that found in the body, incorporating rich components that support drug stability. This characteristic enables ECM scaffolds to provide more comprehensive biomechanics, more stable drug storage environments, and enhanced synergistic therapeutic effects, thereby augmenting the efficacy of individual stem cell-derived exos.

Exo and Microneedle Patches

Microneedle patches, consisting of a base and an array of

micrometer-scale needles, effectively penetrate the skin's physical barrier, breach the stratum corneum, and deliver drugs directly to the dermis. As a result, they are regarded as superior tools for transdermal drug delivery [19]. The needle length of microneedle patches typically ranges from 25 to 2000 micrometers, with dimensions, shapes, and materials frequently modified to suit the intended application [35]. Consequently, microneedles facilitate stem cell-derived exos in achieving precise localization, skin penetration, and sustained drug delivery, offering promising applications in skin care, wound healing, and disease treatment.

Microneedle patches serve as effective absorption-enhancing devices for cosmetic agents, making exo-loaded microneedle patches a promising approach to combat skin aging. Park *et al.* [36] conducted a 12-week clinical study investigating the synergistic effects of stem cell exos and microneedle treatment on facial skin aging. Their research demonstrated the safety and efficacy of the combined product in mitigating signs of aging, significantly advancing the clinical application of exo microneedles in medical aesthetics. In a similar vein, Liang *et al.* [37] assessed the efficacy of human umbilical cord mesenchymal stem cell-conditioned medium (hUC-MSCs-CM) purified exos loaded onto microneedles for enhancing skin brightness and rejuvenation through a randomized controlled clinical trial. The results revealed significant improvements in wrinkle index and melanin index compared to the control group. This minimally invasive and safe combination product shows potential for rapid adoption in dermatological applications.

Furthermore, these stem cell exo-loaded microneedle patches demonstrate efficacy in reversing hypertrophic scars and enhancing wound healing. Meng *et al.* [38] developed exos with elevated expression of miR-141-3p and incorporated them into water-soluble microneedles, resulting in decreased thickness of hypertrophic scars and improved distribution of fibroblasts and collagen fibers. Gan *et al.* [39] incorporated MSC-exos and silver nanoparticles (AgNPs) with antibacterial properties into adhesive microneedle patches, facilitating diabetic wound healing.

Stem cell-derived exos offer an effective approach to treating tissue injury diseases. However, delivering exos precisely to the injury site while minimizing damage to surrounding tissues remains challenging. Micro-needle patches may provide stem cell-derived exos with these essential characteristics, enabling their broad efficacy in various tissue injuries. Fang *et al.* [15] developed a porous microneedle patch (MN-MSC) that efficiently and continuously delivers exos to repair acute spinal cord injuries. This microneedle patch significantly improved the microenvironment of the injured tissue area within seven days of application, promoting blood vessel regeneration. Similarly, Han *et al.* [40] loaded three-dimensional-cultured exos with enhanced efficacy onto a hydrogel-mixed microneedle array patch, achieving in-situ and precise repair of spinal cord injuries. Additionally, Liu *et al.* [41] invented a microneedle array loaded with nitric oxide nano-engines that drive tendon stem cell-derived exos, promoting Achilles tendon healing. As the high molecular weight polymer on the microneedle array degrades, the exos are exposed and released. Concurrently, reactive oxygen species in the microenvironment and nitric oxide produced by the microneedles' nitric oxide synthase generate nitric oxide gas, increasing the penetration depth of exos. This also establishes a foundation for incorporating multifunctional substances to enhance exo delivery on microneedles. Furthermore, MSC-exos microneedle patches demonstrate effectiveness in preventing cardiac fibrosis. Yuan *et al.* [42] loaded exos containing a microRNA-29b mimic with anti-fibrotic activity into gelatin microneedles, effectively preventing excessive cardiac fibrosis after myocardial infarction.

In conclusion, porous microneedle patches incorporating stem cell-derived exos demonstrate exceptional nanoscale dimensions, biocompatibility, and mechanical properties. These characteristics enable precise application at injury sites and facilitate continuous exo delivery. This approach offers a superior perspective compared to the use of exos alone, providing a more effective method for the precise treatment of skin care, wound repair, and superficial diseases.

Exos and Dressings

Medical dressings are frequently employed to create an optimal healing environment for wounds. These dressings encompass various types, including gel dressings, fiber dressings, biological adjuncts, and collagen patches, which are suitable to serve as carriers with a synergistic effect when combined with exos [43]. The integration of stem cell-derived exos into medical dressings results in a composite product that plays a pivotal role in repairing wound damage, mitigating inflammatory responses, and accelerating wound healing processes.

In the realm of full-thickness skin wound repair, Qian *et al.* [44] engineered an asymmetric wet dressing termed CTS-SF/SA/Ag-Exo, which integrates exos with silver nanoparticles. This innovative dressing preserves wound moisture while simultaneously promoting tissue regeneration and exhibiting potent anti-inflammatory properties, specifically targeting wounds resulting from microbial infections. Analogously, Wu *et al.* [45] formulated a chitosan hydrogel dressing incorporating mesenchymal stem cells, designated as Exo/Gel. This formulation demonstrated efficacy in promoting orderly collagen deposition, vascular regeneration, and hair follicle embedding regeneration in a rat wound model. Furthermore, the hydrogel encapsulation synergistically enhanced the wound healing process.

Furthermore, healing wounds induced by diabetes present a significant challenge in both clinical practice and research. To address characteristics such as early wound dehydration and inflammation, bioactive dressings with functions to maintain moisture and provide anti-inflammatory effects could be a promising adjunct for exos in diabetic wound re-

pair. Wang *et al.* [46] loaded MSC-exos onto a thermosensitive polysaccharide-based fluorinated ethylene propylene (FEP) hydrogel dressing, creating a combined product FEP@exo. This product significantly enhanced the proliferation, migration, and blood vessel formation of endothelial cells *in vitro*, accelerating the healing of diabetic wounds. Shiekh *et al.* [47] developed an antioxidant wound dressing named OxOBand, which, after loading with oxygen-rich adipose stem cell-derived exos, promoted the migration of human keratinocytes and fibroblasts, thereby enhancing the development of mature epithelial structures. Similarly, the combined product could also address psoriasis with similar pathogenic mechanisms. The dressing could synergistically provide active ingredients to maintain moisture, promote regeneration, and selectively reverse pathological conditions, suggesting that the combination product may offer a novel approach to the treatment of skin diseases [48]. Additionally, Lin *et al.* [49] used Ag-S coordination to create injectable hydrogels loaded with ADSCs-exos, providing anti-infection and microenvironment protective properties, promoting endometrial regeneration, and restoring fertility. This indicates how medical devices can expand drug delivery to serve the treatment of pathological environments where drugs are difficult to retain. Loading human bone marrow mesenchymal stem cells into hydrogels could also produce promising patches for cartilage regeneration [50]. In conclusion, combined products created by integrating stem cell-derived exos with hydrogels and other biological adjuncts could provide a portable and synergistic novel therapeutic approach in the clinical treatment of various diseases.

Modifying the properties of gel dressings has expanded their application to the field of nerve repair. Yang *et al.* [51] developed a conductive nerve dressing using conductive hydrogels loaded with BDMC-exos to treat diabetic peripheral nerve injuries. Their findings demonstrated that this combined product significantly enhanced peripheral nerve synapse levels, modulated the inflammatory environment, and promoted nerve remodeling, thereby improving motor function in rats. Similarly, Li *et al.* [52] engineered a hydrogel for transporting MSC-exos, achieving synergistic antioxidant and anti-inflammatory regulation of the microenvironment. These investigations offer novel approaches for peripheral nerve damage repair and pain alleviation, substantially broadening the scope of exo-based treatments for various diseases by leveraging the properties of dressings.

Exo And Filling And Restoration Materials

Medical devices frequently incorporate fillers for diverse applications, including bone repair, tissue healing, and general surgical implants [53]. The integration of stem cell-derived exos with these fillers results in a combination product that leverages the mechanical strength of the inorganic filler to provide direct physical support to traumatized bone tissue. Simultaneously, this product utilizes the contents of exos for complementary tissue repair. Consequently, this approach shows significant potential in fields such as bone regeneration, tissue healing, and aesthetic surgery.

Stem cell-derived exo fillers serve as critical materials for orthopedic repair, offering both structural support and promotion of bone formation, thereby aiding in the restoration of normal mobility. Teotia *et al.* [53] utilized nanostructured calcium sulfate-hydroxyapatite cement as a carrier for MSC-exos, implanting it at critical defect sites in rat tibiae. This approach facilitated the direct delivery of exos to the defect site, promoting their gradual absorption and enhancing bone formation while the filler provided a porous structure. This study presents an innovative strategy for combining stem cell-derived exos with inorganic fillers to create combination products. In a similar vein, Gandolfi *et al.* [54] incorporated adipose-derived mesenchymal stem cell-derived exos onto porous bone fillers, establishing a favorable environment for bone formation. Additionally, Swanson *et al.* [55] integrated exos from human dental pulp stem cells into calcium hydroxide paste and mineral trioxide aggregate, common dental fillers, resulting in the formation of a restorative dentin bridge over an 8–12-week release period. Overall, filler-based combination products demonstrate significant potential in promoting bone regeneration. Unlike scaffold materials, these combination products can directly provide mechanical support to damaged bone tissue through the material's inherent strength, offering a more immediate and direct supportive effect, making them particularly suitable for large wounds that are challenging to heal naturally. However, their tissue compatibility requires optimization through coating with stem cell-derived exos, and their capacity to induce autologous bone tissue regeneration is comparatively limited.

Secondly, stem cell-derived exo fillers demonstrate significant efficacy in supporting and promoting tissue repair in challenging large wounds. Lee *et al.* [56] developed a composite filler by incorporating MSC-exos into hyaluronic acid. Injection of this combination product in a mouse dermal filler model resulted in thicker tissue layers, increased vascularization, and enhanced collagen fiber deposition, thus promoting wound healing. Park *et al.* [57] designed an optimized filler composition comprising type I collagen, fibronectin, and hyaluronic acid, which also shows promise for stem cell-derived exo fillers.

Stem cell-derived exo fillers represent an innovative approach to contemporary aesthetic filling techniques. Post-application, these fillers demonstrate a significant reduction in facial wrinkles while enhancing skin smoothness and elasticity. In comparison to conventional fillers, exo-based alternatives offer several advantages, including extended longevity, enhanced safety profiles, reduced rejection rates, and superior biological maintenance effects on skin collagen and elastic tissues. Nevertheless, exo fillers necessitate more comprehensive safety evaluations to mitigate potential adverse effects, such as allergic reactions, which may impact users.

In conclusion, stem cell-derived exo fillers combined with various biomaterials present an innovative and prom-

ising approach for bone regeneration, tissue healing, and aesthetic treatments. These combination products demonstrate significant potential to transform current practices in medical device development and clinical applications.

Conclusion and Future Directions

In conclusion, various medical devices can potentially optimize stem cell-derived exos for treating diverse medical conditions and enhancing patient outcomes. The integration of medical devices with stem cell-derived exos presents significant potential for therapeutic applications, regenerative medicine, and aesthetic procedures, facilitating the translation of multicellular-derived exos into clinical practice. The comprehensive investigation of combination products has also broadened the utilization of other natural sources for drugs and devices. Building upon the current research foundation, future studies may focus on developing more advanced production technologies for combination products, expanding their applications across various diseases, and refining the evaluation mechanisms for these integrated solutions.

Firstly, the utilization of high-precision printing technology to enhance the accuracy and intricacy of scaffolds, blood vessels, microneedles, and other medical devices can better achieve stable support and controlled release of stem cell-derived exos. This approach represents a promising direction for the technological advancement of regenerative medicine combination products in the future. Addressing the efficient loading of stem cell-derived exos and maintaining their stability in medical devices remains a technical challenge to be optimized.

Secondly, selecting medical devices with specific properties tailored to the disease state to accommodate stem cell-derived exos from various sources will expand the application forms of combination products. This review has discussed research on functional materials with neural conductivity properties that confer electrical conductivity to stem cell-derived exos, as well as the utilization of fish scale materials to enhance the extensibility and coverage of stem cell-derived exos. Future studies may explore medical devices with more adaptive functions as platforms for stem cell exo-based therapeutics, thereby enriching the physical application properties of stem cell-derived exos.

Finally, enhancing evaluation methods and regulatory frameworks remains a crucial aspect of combination product development. The incorporation of medical devices significantly alters the release and metabolic properties of drugs, necessitating the establishment of appropriate testing methods and regulations tailored to the components' nature. Moreover, both drugs and medical devices must adhere to relevant laws and regulations for registration or filing purposes.

References

[1] Van Niel G, D'Angelo G, Raposo G. Shedding light on the cell biology of extracellular vesicles [J]. *Nat Rev Mol Cell Biol*, 2018, **19**: 213-28.

[2] Théry C, Witwer KW, Aikawa E, *et al*. Minimal information for studies of exosomes 2018 (MISEV2018): a position statement of the international society for exosomes and update of the MISEV2014 guidelines [J]. *J Extracell Vesicles*, 2018, **7**: 1535750.

[3] Kalluri R, LeBleu VS. The biology, function, and biomedical applications of exosomes [J]. *Science*, 2020, **367**: 6478.

[4] Riazifar M, Mohammadi MR, Pone EJ, *et al*. Stem cell-derived exosomes as nanotherapeutics for autoimmune and neurodegenerative disorders [J]. *ACS Nano*, 2019, **13**: 6670-6688.

[5] Mead B, Tomarev S. Extracellular vesicle therapy for retinal diseases [J]. *Prog Retin Eye Res*, 2020, **79**: 100849.

[6] Tenchov R, Sasso JM, Wang X, *et al*. Exosomes─nature's lipid nanoparticles, a rising star in drug delivery and diagnostics [J]. *ACS Nano*, 2022, **16**(11): 17802-17846.

[7] Yang Y, Hong Y, Cho E, *et al*. Extracellular vesicles as a platform for membrane-associated therapeutic protein delivery [J]. *J Extracell Vesicles*, 2018, (7): 1440131.

[8] Sun Y, Liu G, Zhang K, *et al*. Mesenchymal stem cells-derived exosomes for drug delivery [J]. *Stem Cell Res Ther*, 2021, **12**: 1-15.

[9] Tehrani F, Teymourian H, Wuerstle B, *et al*. An integrated wearable microneedle array for the continuous monitoring of multiple biomarkers in interstitial fluid [J]. *Nat Biomed Eng*, 2022, **6**: 1214-1224.

[10] Aronson JK, Heneghan C, Ferner RE. Medical devices: definition, classification, and regulatory implications [J]. *Drug Saf*, 2020, **43**: 83-93.

[11] Yu J, Wang J, Zhang Y, *et al*. Glucose-responsive insulin patch for the regulation of blood glucose in mice and minipigs [J]. *Nat Biomed Eng*, 2020, **4**: 499-506.

[12] Ricles LM, Coburn JC, Prima M Di, *et al*. Regulating 3D-printed medical products [J]. *Sci Trans Med*, 2018, **6521**: 1-6.

[13] Alvarez-Lorenzo C, Concheiro A. Smart drug release from medical devices [J]. *J Pharmacol Exp Ther*, 2019, **370**: 544-554.

[14] Papi A, Chipps BE, Beasley R, *et al*. Albuterol–budesonide fixed-dose combination rescue inhaler for asthma [J]. *N Engl J Med*, 2022, **386**: 2071-2083.

[15] Fang A, Wang Y, Guan N, *et al*. Porous microneedle patch with sustained delivery of exosomes mitigates severe spinal cord injury [J]. *Nat Commun*, 2023, **14**: 1-17.

[16] Hu S, Li Z, Shen D, *et al*. Exosome-eluting stents for vascular healing after ischaemic injury [J]. *Nat Biomed Eng*, 2021, **5**: 1174-1188.

[17] Kim SH, Hong H, Ajiteru O, *et al*. 3D bioprinted silk fibroin hydrogels for tissue engineering [J]. *Nat Protoc*, 2021, **16**: 5484-5532.

[18] Zhang J, Tong D, Song H, *et al*. Osteoimmunity-regulating biomimetically hierarchical scaffold for augmented bone regeneration [J]. *Adv Mater*, 2022, **34**: 1-18.

[19] Wang Z, Liang X, Wang G, *et al*. Emerging bioprinting for wound healing [J]. *Adv Mater*, 2023, **2023**: 2304738.

[20] Kang Y, Xu C, Meng L, *et al*. Exosome-functionalized magnesium-organic framework-based scaffolds with osteogenic, angiogenic and anti-inflammatory properties for accelerated bone regeneration [J]. *Bioact Mater*, 2022, **18**: 26-41.

[21] Su N, Hao Y, Wang F, *et al*. Mesenchymal stromal exosome–functionalized scaffolds induce innate and adaptive immunomodulatory responses toward tissue repair [J]. *Sci Adv*, 2021, **7**: 1-12.

[22] Liu A, Lin D, Zhao H, *et al*. Optimized BMSC-derived osteoinductive exosomes immobilized in hierarchical scaffold *via* lyophilization for bone repair through Bmpr2/Acvr2b competitive receptor-activated Smad pathway [J]. *Biomaterials*, 2021, **272**: 120718.

[23] Swanson WB, Zhang Z, Xiu K, *et al*. Scaffolds with controlled release of pro-mineralization exosomes to promote craniofacial bone healing without cell transplantation [J]. *Acta Biomater*, 2020, **118**: 215-232.

[24] Freedman BR, Mooney DJ. Biomaterials to mimic and heal connective tissues [J]. *Adv Mater*, 2019, **31**: 1-27.
[25] Yurchenco PD. Basement membranes: cell scaffoldings and signaling platforms [J]. *Cold Spring Harb Perspect Biol*, 2011, **3**: 1-27.
[26] Zhang L, Fan C, Hao W, *et al*. NSCs migration promoted and drug delivered exosomes-collagen scaffold *via* a bio-specific peptide for one-step spinal cord injury repair [J]. *Adv Healthc Mater*, 2021, **10**: 1-11.
[27] Wang Y, Zhang Y, Li T, *et al*. Adipose mesenchymal stem cell derived exosomes promote keratinocytes and fibroblasts embedded in collagen/platelet-rich plasma scaffold and accelerate wound healing [J]. *Adv Mater*, 2023, 35.
[28] Ding L, Yan G, Wang B, *et al*. Transplantation of UC-MSCs on collagen scaffold activates follicles in dormant ovaries of POF patients with long history of infertility [J]. *Sci China Life Sci*, 2018, **61**: 1554-1565.
[29] Tang H, Li J, Wang H, *et al*. Human umbilical cord mesenchymal stem cell-derived exosomes loaded into a composite conduit promote functional recovery after peripheral nerve injury in rats [J]. *Neural Regen Res*, 2024, **19**: 900-907.
[30] Wang Y, Kong B, Chen X, *et al*. BMSC exosome-enriched acellular fish scale scaffolds promote bone regeneration [J]. *J Nanobiotechnol*, 2022, **20**: 1-11.
[31] Senger DR, Davis GE. Angiogenesis [J]. *Cold Spring Harb Perspect Biol*, 2011, **3**: a005090.
[32] Jiang S, Tian G, Yang Z, *et al*. Enhancement of acellular cartilage matrix scaffold by Wharton's jelly mesenchymal stem cell-derived exosomes to promote osteochondral regeneration [J]. *Bioact Mater*, 2021, **6**: 2711-2728.
[33] Kang Y, Xu J, Meng L, *et al*. 3D bioprinting of dECM/Gel/QCS/nHAp hybrid scaffolds laden with mesenchymal stem cell-derived exosomes to improve angiogenesis and osteogenesis [J]. *Biofabrication*, 2023, **15**: 024103.
[34] Chen P, Zheng L, Wang Y, *et al*. Desktop-stereolithography 3D printing of a radially oriented extracellular matrix/mesenchymal stem cell exosome bioink for osteochondral defect regeneration [J]. *Theranostics*, 2019, **9**: 2439-2459.
[35] Jamaledin R, Yiu CKY, Zare EN, *et al*. Advances in antimicrobial microneedle patches for combating infections [J]. *Adv Mater*, 2020, **32**: 1-29.
[36] Park GH, Kwon HH, Seok J, *et al*. Efficacy of combined treatment with human adipose tissue stem cell-derived exosome-containing solution and microneedling for facial skin aging: a 12-week prospective, randomized, split-face study [J]. *J Cosmet Dermatol*, 2023, **22**: 3418-3426.
[37] Liang X, Li J, Yan Y, *et al*. Efficacy of microneedling combined with local application of human umbilical cord-derived mesenchymal stem cells conditioned media in skin brightness and rejuvenation: a randomized controlled split-face study [J]. *Front Med*, 2022, **9**: 1-8.
[38] Meng S, Wei Q, Chen S, *et al*. MiR-141-3p-functionalized exosomes loaded in dissolvable microneedle arrays for hypertrophic scar treatment [J]. *Small*, 2023, **2305374**: 1-17.
[39] Gan J, Zhang X, Ma W, *et al*. Antibacterial, adhesive, and MSC exosomes encapsulated microneedles with spatio-temporal variation functions for diabetic wound healing [J]. *Nano Today*, 2022, **47**: 101630.
[40] Han M, Yang H, Lu X, *et al*. Three-dimensional-cultured MSC-derived exosome-hydrogel hybrid microneedle array patch for spinal cord repair [J]. *Nano Lett*, 2022, **22**: 6391-6401.
[41] Liu A, Wang Q, Zhao Z, *et al*. Nitric oxide nanomotor driving exosomes-loaded microneedles for achilles tendinopathy healing [J]. *ACS Nano*, 2021, **15**: 13339-13350.
[42] Yuan J, Yang H, Liu C, *et al*. Microneedle patch loaded with exosomes containing microRNA-29b prevents cardiac fibrosis after myocardial infarction [J]. *Adv Healthc Mater*, 2023, **12**: 1-12.
[43] Hickman DSA, Pawlowski CL, Sekhon UDS, *et al*. Biomaterials and advanced technologies for hemostatic management of bleeding [J]. *Adv Mater*, 2018, **30**: 1-40.
[44] Qian Z, Bai Y, Zhou J, *et al*. A moisturizing chitosan-silk fibroin dressing with silver nanoparticles-adsorbed exosomes for repairing infected wounds [J]. *J Mater Chem B*, 2020, **8**: 7197-7212.
[45] Wu D, Tao S, Zhu L, *et al*. Chitosan hydrogel dressing loaded with adipose mesenchymal stem cell-derived exosomes promotes skin full-thickness wound repair [J]. *ACS Appl Bio Mater*, 2024, **7**: 1125-1134.
[46] Wang M, Wang C, Chen M, *et al*. Efficient angiogenesis-based diabetic wound healing/skin reconstruction through bioactive antibacterial adhesive ultraviolet shielding nanodressing with exosome release [J]. *ACS Nano*, 2019, **13**: 10279-10293.
[47] Shiekh PA, Singh A, Kumar A. Exosome laden oxygen releasing antioxidant and antibacterial cryogel wound dressing OxOBand alleviate diabetic and infectious wound healing [J]. *Biomaterials*, 2020, **249**: 120020.
[48] Seetharaman R, Mahmood A, Kshatriya P, *et al*. Mesenchymal stem cell conditioned media ameliorate psoriasis vulgaris: a case study [J]. *Case Rep Dermatol Med*, 2019, 8309103.
[49] Lin J, Wang Z, Huang J, *et al*. Microenvironment-protected exosome-hydrogel for facilitating endometrial regeneration, fertility restoration, and live birth of offspring [J]. *Small*, 2021, **17**: 1-13.
[50] Liu X, Yang Y, Li Y, *et al*. Integration of stem cell-derived exosomes with in situ hydrogel glue as a promising tissue patch for articular cartilage regeneration [J]. *Nanoscale*, 2017, **9**: 4430-4438.
[51] Yang Q, Su S, Liu S, *et al*. Exosomes-loaded electroconductive nerve dressing for nerve regeneration and pain relief against diabetic peripheral nerve injury [J]. *Bioact Mater*, 2023, **26**: 194-215.
[52] Li L, Zhang Y, Mu J, *et al*. Transplantation of human mesenchymal stem-cell-derived exosomes immobilized in an adhesive hydrogel for effective treatment of spinal cord injury [J]. *Nano Lett*, 2020, **20**: 4298-4305.
[53] Teotia AK, Qayoom I, Singh P, *et al*. Exosome-functionalized ceramic bone substitute promotes critical-sized bone defect repair in rats [J]. *ACS Appl Bio Mater*, 2021, **4**: 3716-3726.
[54] Gandolfi MG, Gardin C, Zamparini F, *et al*. Mineral-doped poly(L-lactide) acid scaffolds enriched with exosomes improve osteogenic commitment of human adipose-derived mesenchymal stem cells [J]. *Nanomaterials*, 2020, **10**: 432.
[55] Swanson WB, Gong T, Zhang Z, *et al*. Controlled release of odontogenic exosomes from a biodegradable vehicle mediates dentinogenesis as a novel biomimetic pulp capping therapy [J]. *J Control Release*, 2020, **324**: 679-694.
[56] Lee JH, Won YJ, Kim H, *et al*. Adipose tissue-derived mesenchymal stem cell-derived exosomes promote wound healing and tissue regeneration [J]. *Int J Mol Sci*, 2023, **24**(13): 10434.
[57] Park C, Lee OH, Park JJ, *et al*. Self-assembled adipose-derived mesenchymal stem cells as an extracellular matrix component- and growth factor-enriched filler [J]. *Front Cell Dev Biol*, 2023, **11**: 1-13.

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