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REVIEW

Mesenchymal Stem Cells-Derived Exosomes: Next-Generation Nanomedicines Toward Scarless Wound Healing

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Abstract: The process of wound healing is intricate and, once disrupted, results in scar formation. Scar formation has negative physiological and psychological impacts on patients in addition to impeding the restoration of skin integrity and function. Increasing evidence indicates that factors such as angiogenesis, ECM deposition, and inflammation are all associated with scar formation. Given their excellent immunomodulatory and regenerative properties, mesenchymal stem cell-derived exosomes (MSCs-Exos) are increasingly favored in inhibiting scar formation during wound healing. This review begins with a summary of the key mechanisms of wound healing and scar formation, followed by the application of MSCs-Exos in attenuating the pathological process of scar formation, as well as its potential mechanisms of action. In addition, the current status and development prospects of engineered exosomes and hydrogel-combined exosomes in scar inhibition are further discussed. Finally, we evaluate the current challenges of using exosomes for scarless wound healing, including manufacturing standardization, dosing, delivery systems, and the lack of large-scale clinical data, which hold the potential to bridge the gap between the laboratory and the clinical.

Keywords: mesenchymal stem cells, exosomes, engineered nanoparticle, hydrogel, scarless wound healing

Introduction

Scar tissue not only leads to aesthetic defects, but also impairs skin and joint function by generating neuropathic pain, surface irregularities, itching, stiffness, and disabling contracture dysfunction, resulting in a substantial economic burden on society.[1,2] Common causes include burn, acne, trauma, folliculitis, vaccination, surgery, skin piercing, herpes zoster infection, pressure ulcers, venous ulcers of the lower limbs, and diabetic foot ulcers.[3] Traditional scar treatments include negative pressure wound therapy, surgical excision, physical therapy, radiation therapy, gene therapy, and glucocorticoid injection.[4–8] Although there are various methods for scar treatment, due to the complexity and high recurrence rate of scars, scarless wound healing remains difficult to achieve. In addition to traditional treatment methods, emerging biomedical technologies, including stem cell technology and nanotechnology, offer effective alternatives for preventing scar formation.[9] These approaches regulate the wound microenvironment in a non-invasive manner but present issues of biosafety and immune rejection.

Exosomes are nanoscale extracellular vesicles that have a diameter ranging from 30–150 nm and are released by various cells, which act as intercellular communication mediators.[10] In comparison to synthetic transporters, exosomes exhibit greater stability, ease of production, and reduced cost, making them effective carriers of molecular cargo and optimal candidates for therapeutic applications in regenerative medicine.[11] Mesenchymal stem cells-derived exosomes (MSCs-Exos) are structurally and morphologically similar to other exosomes, they are increasingly favored in preventing scar formation during wound healing because of their immunomodulatory and regenerative functions.[12,13] As cell-free

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therapies, MSCs-Exos primarily regulate the recipient cells via their cargos, which include lipids, nucleic acids, and proteins. The wound healing process is a complex, multi-factorial process involving immune regulation, extracellular matrix remodeling, and angiogenesis. MSCs-Exos may promote wound healing by regulating one or multiple factors.[14,15]

While MSCs-Exos have a positive impact on scar formation inhibition, heterogeneity, scalability, and storage issues hinder their clinical translation. In addition, MSCs-Exos exhibit drawbacks that may compromise their therapeutic effectiveness, including low yields, impurities, inadequate targeting and low drug delivery rates.[16,17] Engineered MSCs-Exos are potential exosomes that have been modified, loaded, or edited to minimize scar formation and promote wound healing. Engineered MSCs-Exos can boost purity, yield, and bioactivity,[18,19] while also facilitating the wound healing process by loading diverse molecules including drugs, growth factors, or cytokines to target particular pathways.[20] As a result, engineered MSCs-Exos are a feasible method for increasing their bioactivity and boosting repair efficiency in minimizing scar formation.

Meanwhile, the application of exosomes in scarless wound healing is still challenging due to their rapid clearance and limited half-life. In addition, given that the wound healing process generally requires a long time, the activity and function of free exosomes will be correspondingly damaged, which is another issue we need to solve.[21] Hydrogels are highly hydrophilic and biocompatible, which can provide abundant storage space for exosomes while maintaining biostability. The encapsulated exosomes are gradually released as the hydrogels degrade in wound microenvironment to exert anti-scarring effects.[22,23] Hydrogel dressings have been widely developed for wound healing; however, their market applicability is determined by factors such as cost control capability and market application value. Therefore, promoting the transformation from low cost to high value is essential for wound healing materials.

This article first reviews the pathological process of scar formation during wound healing, followed by an explanation of MSCs-Exos in inhibiting the pathological process of scar formation, along with their potential mechanism of action. Besides, the current status and future prospects of engineered MSCs-Exos and hydrogel-combined MSCs-Exos in scar inhibition are further discussed (Figure 1). Finally, we assess current challenges in scarless wound healing and provide fundamental insights into future clinically relevant directions for MSCs-Exos-based therapy.

Scar Formation in Wound Healing Process

Scar formation often occurs during wound healing. Understanding the wound healing process is crucial for effective treatment of keloids and hypertrophic scars. Wound healing is a complicated procedure involving four interconnected stages: hemostasis, inflammation, proliferation, and remodeling, which involve the secretion of biomolecules and cytokines by various cells (Figure 2).[24,25]

Wound Healing Phases

Hemostasis happens in a matter of seconds to minutes.[26] At this stage, the damaged vessels constrict, platelets adhere and aggregate, and the coagulation pathway is initiated by exposing the subendothelial matrix, forming fibrin plugs that provides a framework for inflammatory cells. Subsequently, cytokines recruit immune cells, including neutrophils and macrophages, to initiate the inflammatory phase.[27]

The inflammatory stage begins following a skin injury and typically lasts for hours to days. Extracellular matrix (ECM) and platelet plugs are formed at this stage to close the wound, prevent blood loss and infection, remove necrotic tissue, and direct cell migration.[28]

The proliferation stage usually lasts for weeks and is marked by fibroblast migration, ECM and collagen generation, angiogenesis, granulation formation, and epithelialization. First of all, fibroblasts start to move by binding to matrix component like fibronectin through integrity receptor. Subsequently, fibroblasts release collagenase, matrix metalloproteinase, and gelatinase to break down the ECM, further enhancing cell movement. Following fibroblast migration, TGF-β and platelet-derived growth factor (PDGF) promote ECM formation. Meanwhile, damaged blood vessels are substituted by new ones via angiogenesis induced by hypoxia-inducible factor (HIF), vascular endothelial growth factor (VEGF), and PDGF. The process of epithelialization entails the loss of contact inhibition of epithelial cells and migration from the wound edge into the wound region.[29]

Figure 1 Schematic illustration of this review regarding background knowledge and the mechanism and application of MSC-Exos for scarless wound healing. Background knowledge includes four interrelated stages: hemostasis, inflammation, proliferation, and remodeling. The mechanism represents the mechanism of scar formation inhibition. Their applications include natural exosomes, engineered exosomes, and hydrogel-exosome system.

Remodeling is the last stage of wound healing, which can take months to years and results primarily in keloid and hypertrophic scar formation. During the remodeling stage, type III collagen turns to type I collagen to enhance matrix density and stability.[30] More importantly, the abnormal fibroblast proliferation and differentiation into myofibroblasts, along with the imbalance between ECM production and breakdown, primarily contribute to pathological scar formation.

Physical Factors on Scar Formation

Mechanical Forces

Scar development and tissue healing are influenced by the mechanical forces operating on the wound area.[31] Hence, when the wound is subjected to continuous increase of mechanical force, when there is a marked increase in scarring

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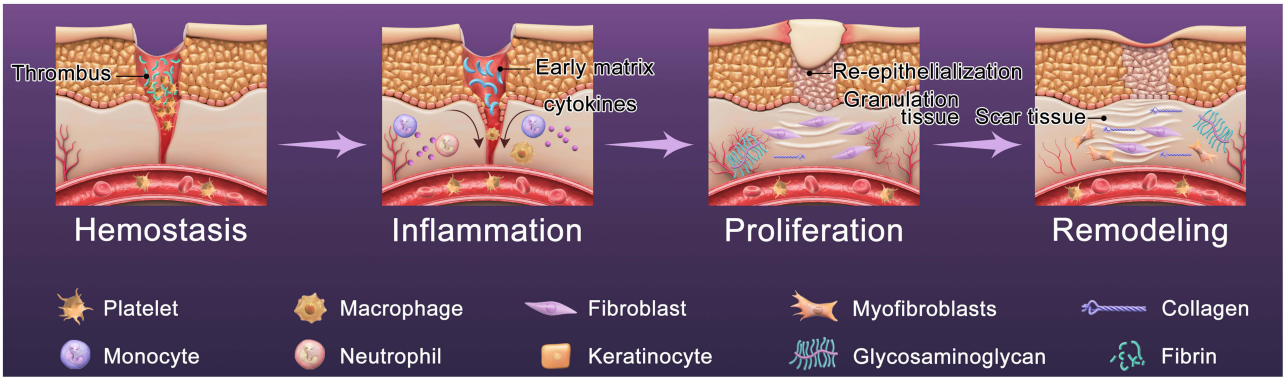

Figure 2 The four stages of wound healing, including hemostasis, inflammation, proliferation and remodeling.

after wound healing.[32] On the contrary, a reduction of mechanical force at wound site results in decreased scars. Research has demonstrated that alleviating mechanical stress of wound area using tension shielding helps prevent scarring.[33] In addition, scar formation is significantly affected by numerous mechanical forces during wound healing, including compressive force, osmotic force, and shear force. Particularly, wounds on the sternum, joints, and back are subjects to severe mechanical loads, resulting in an extensive scar area post-healing.[34] When the mechanoreceptors on the cell membrane sense external mechanical forces, this signal is conveyed to the cell via the cell membrane. Subsequently, intracellular signaling pathways are triggered, inducing fibrosis and resulting in the formation of hypertrophic scars.[35]

Wound Depth

In addition to mechanical forces, scar formation also depends on the wound depth, which refers to the distance from the epidermis to the interior. When the wound only hurts the epidermis and does not affect the underlying tissues, such as abrasions, minor burns, and friction, it typically leaves no scars. What's more, dermis wounds like shallow degree burns and incisions tend to leave fewer visible scars. However, destructive injuries and severe burns that invade the dermis and even reach the subcutaneous tissue and deep tissue frequently leave visible scars and impair tissue function.[36] Generally, tissue repair restores the original tissue instead of leaving a scar.[37]

Hence, to attain scarless wound healing, it is imperative to investigate the mechanisms underlying scar formation more thoroughly. The following provides an overview of numerous factors that affect scar formation.

Scar Formation Pathogenesis

Keloids and hypertrophic scars share similar pathological processes to some extent, including proliferation, apoptosis inhibition, ECM deposition, angiogenesis, inflammatory response, and epithelial to mesenchymal transition (EMT),[38,39] which may suggest a potential therapeutic mechanism of exosomes in scar prevention.

Proliferation and Apoptosis Inhibition

Excessive proliferation of fibroblasts and inhibition of apoptosis are essential for the formation and progression of hypertrophic scars and keloids. First of all, the sustained activation of TGF-β/Smad pathway facilitates fibroblast proliferation, essential for collagen production during scar formation. In addition, Wnt5a, Wnt10a, and β-Catenin also promote fibroblast proliferation through modulating the Wnt/β-Catenin signaling.[40–42] Finally, higher levels of c-Myc and anti-apoptotic proteins Bcl-2, along with c-Fos and c-Jun that promote sustained fibroblast growth signals, and lower levels of anti-apoptotic protein P53 appeared in keloids, all of which could contribute to scar formation and progression.[43,44]

ECM Deposition

Typically, excessive fibrosis and collagen deposition occur in scar tissues. It has been reported that cytokines including IL-6 and TGF-β1 may promote the accumulation of fibronectin, collagen, and fibrotic proteins in scar fibroblasts.[45,46] Furthermore, matrix metalloproteinases (MMPs) have complicated functions in the formation and development of

abnormal scars. For one thing, MMPs can be activated by Wnt/β-Catenin pathway inhibitor, thereby attenuating collagen formation in normal fibroblasts and scar tissues.[47] For another, MMP-2 levels were increased in collagen bundle areas, which may contribute to scar fibroblasts invasion and collagen bundle remodeling through degrading ECM.[48]

Angiogenesis

As previously stated, angiogenesis supplies necessary oxygen and nutrients for wound healing during the proliferation phase. Studies have demonstrated that hypertrophic scar myoblasts may generate microvesicles that promote proliferation, migration, and assembly of endothelial cells, resulting in excessive scar vascularization.[49] In addition, either VEGF and its receptor VEGFR or PDGF and its receptor PDGFR-α are overexpressed in scar-derived fibroblasts, phagocytes, epidermal cells, endothelial cells, and adventitial cells, maintaining metabolism and vascularization for nutrient delivery by facilitating the growth, migration, and assembly of endothelial cells.[50]

Inflammation

All pathological scars share the trait of chronic inflammation. Rapid inflammatory responses can avoid infection from causing damage to the body during wound healing, but it may also result in scar formation.[37] Specifically, some activated inflammatory cells promote the massive secretion of ECM components, such as collagen, by regulating the activity of fibroblasts and myofibroblasts, causing ECM deposition and cross-linking, and eventually resulting in pathological scar formation.[51,52] Additionally, inflammation severity is closely associated to scar formation, and an excessive inflammatory response might even contribute to the formation of pathological scarring.[53]

EMT

EMT has a significant role in the advancement of scar formation.[54,55] With regard to pathological scars, EMT may facilitate continuous transition of epithelial cells into myofibroblasts and fibroblasts, leading to excessive ECM accumulation, especially collagen, as well as altered cell behavior.[56] Research indicated that hypertrophic scar fibroblasts upregulated EMT markers including vimentin and N-cadherin in hypertrophic scar tissue by secreting exosomes.[57,58] What's more, the JAK/STAT signaling was regulated to promote the IL-6-dependent EMT in keloid pathogenesis.[59] It was reported that keloid keratinocytes may also adopt an EMT phenotype in hypoxic environments, demonstrating elevated invasiveness,[60] while the antifibrotic agent pirfenidone might diminish the EMT-like phenotype in in these cells.[61]

MSCs-Exos in Inhibiting Scar Formation

With a deeper understanding of how scars form, different technologies have been developed to reduce scar or promote scar removal. As mentioned above, MSC-Exos positively influence the inhibition of scar formation (Figure 3). In this section, we will specifically demonstrate how MSC-Exos inhibit the pathological process of scar formation (Table 1).

Proliferation Suppression and Apoptosis Promotion

S Research indicates that stem cell exosomes can block the TGF-β1/Smad signaling, making keloid fibroblasts more susceptible to apoptosis and attenuating their migration and proliferation.[65] Yang et al applied conditioned medium containing adipose-derived stem cells (ADSCs) exosomes to suppress keloid fibroblast proliferation and promote apoptosis via the cyclooxygenase-2/prostaglandin E2 signaling.[62] In addition, Fang et al found that conditioned medium containing bone marrow mesenchymal stem cells (BMSCs) exosomes could suppress the proliferation and migration of keloid fibroblasts and hypertrophic scar fibroblasts.[63] Similarly, Arno et al demonstrated that conditioned medium containing umbilical cord mesenchymal stem cells (HucMSCs) exosomes significantly inhibited the proliferation of keloid fibroblasts while causing no significant change in apoptotic rate.[77]

However, stem cell exosomes may also have a dual role in tissue generation. Ren et al found that ADSCs-derived exosomes promoted cell growth at 5 and 10 μg/mL,[78] while Li et al found that cell proliferation was inhibited at 100 μg/mL.[64] One possible explanation for the dual functions of stem cell exosomes in tissue generation is the heterogeneity of fibroblasts and their microenvironment. Fibroblasts exhibit different functions and responses to growth factors at different phases of wound healing.[79] Therefore, exosomes may exhibit different effects on fibroblasts, boosting tissue

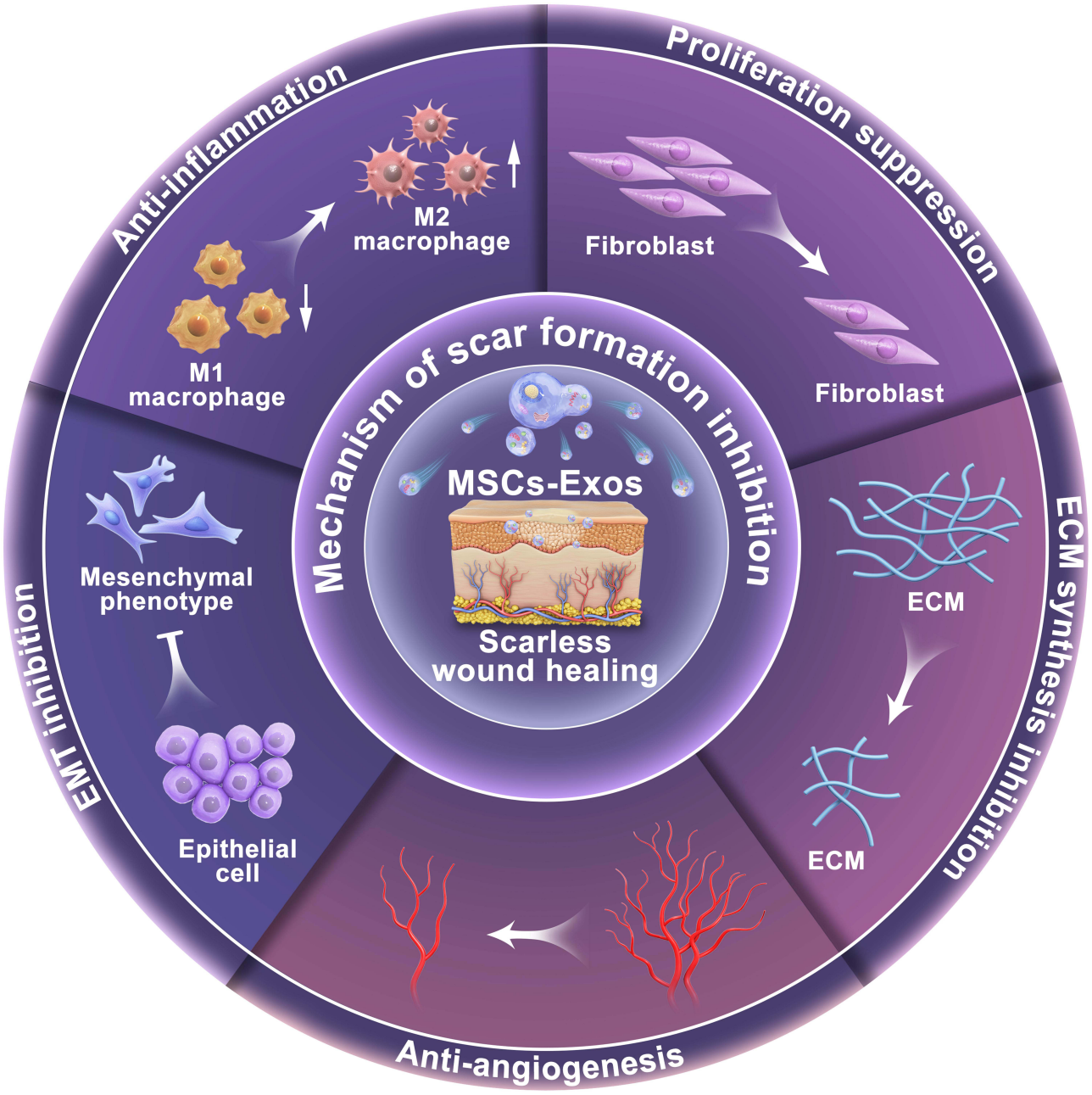

Figure 3 Possible mechanisms of MSC-Exos in scar formation, including proliferation suppression, ECM synthesis inhibition, anti-angiogenesis, anti-inflammation and EMT inhibition.

regeneration in the early stage and suppressing excessive ECM generation to avoid scar formation in the later remodeling stage.[80,81] Finally, given the complexity of the wound healing process, it is necessary to conduct in-depth research on the role of stem cell exosomes in different stages of wounding healing as well as different fibroblasts subtypes, including myofibroblasts, papillary fibroblasts, and reticular fibroblasts.

ECM Synthesis Inhibition

Hypertrophic scars and keloids are fibroproliferative disorders distinguished by the abnormal ECM deposition.[82,83] Research indicates that stem cell exosomes exert anti-fibrotic impacts on keloid and hypertrophic scar fibroblasts. To confirm the antifibrotic effects of stem cell exosomes, Wang et al examined the mRNA levels of ECM-associated genes in keloid fibroblasts. The findings demonstrated that the ADSCs conditioned medium significantly inhibited the mRNA

Table 1 Representative Example of MSCs-Exos Inhibiting the Pathological Process of Scar Formation

Mechanism	Exos Source	Exos Molecule	Disease Model	Signal Pathway	Reference
Proliferation inhibition and apoptosis promotion	ADSCs	–	BALB/c nude mouse keloid transplantation model	COX-2/PGE2 cascade activation	[62]
	BMSCs	-	-	Paracrine signaling	[63]
ECM inhibition	ADSCs	-	-	TGF-β2/Smad3	[64]
	ADSCs			TGF-β1/Smad3	[65]
	ADSCs	miR-29a	Kunming male mouse scald skin model	TGF-β2/Smad3	[66]
	ADSCs	miR-192-5p	BALB/c mouse full-thickness cutaneous wound	miR-192-5p/IL-17RA/Smad	[67]
	hAMSCs	miR-let-7d	Rabbit ear hypertrophic scar model	DMT1/SLC11A2	[68]
Anti-angiogenesis	BMSCs	miR-16	-	Paracrine signaling	[69]
	BMSCs	miR-100	-	mTOR/HIF-1α/VEGF	[70]
	ADSCs	miR-126-5p miR-31-5p miR-21-3p	BALB/c diabetic nude mouse full-thickness cutaneous wound	PI3K/AKT	[71]
Anti-inflammation	BMSCs	melatonin	SD diabetic rat full-thickness cutaneous wound model	PTEN/AKT	[72]
	ADSCs	-	BALB/C mouse sepsis model	Nrf2/HO-1	[73]
EMT inhibition	BMSCs	miR-466f-3p	C57BL/6 mouse radiation-induced lung injury model	AKT/GSK3β	[74]
	HucMSCs	miR-15a-5p	BALB/c nude mouse xenograft tumor model	miR-15a-5p/CHEK1	[75]
	MSCs	miR-100	-	miR-100/mTOR/miR-143	[76]

levels of collagen 1, TIMP-1, and PAI-1.[84] Meanwhile, Wu et al found that exosomes from ADSCs attenuated keloid fibroblasts proliferation and collagen synthesis through blocking the TGF-β1/Smad signaling, leading to reduced scar formation.[65] What's more, increasing evidence suggests that stem cell exosome-enriched microRNAs play a critical role in anti-fibrosis and ECM synthesis inhibition.[85–87] For instance, Yuan et al demonstrated that miR-29a-modified ADSCs-Exos attenuated fibrosis of hypertrophic scar fibroblasts and ECM synthesis through downregulating the TGF-β2/Smad3 signaling.[66] What's more, Li et al revealed that ADSCs-Exos alleviated hypertrophic scar fibrosis, promoted wound healing and attenuated collagen accumulation in vivo.[67] Furthermore, there are also studies that treat hypertrophic scars in terms of iron metabolism for the first time, potentially offering a new direction for fibrotic disease treatment. For example, a study conducted by Zhao et al applied human amniotic epithelial cell-derived miR-let-7d to attenuate hypertrophic scar fibrosis by inhibiting iron uptake via targeting DMT1, while the decreased iron level further suppressed ECM deposition.[68] In summary, MSCs-Exos play an important anti-fibrotic role in keloid and hypertrophic scar fibroblasts, thereby inhibiting ECM deposition.

Anti-Angiogenesis

Angiogenesis supplies essential nutrients and oxygen and for wound healing. However, continued angiogenesis further promotes scar formation by supplying nutrients, similar to tumors.[88,89] Primarily, we will address the function of stem cell exosomes in tumor angiogenesis in this section.

The study conducted by Wang et al first demonstrated that ADSCs-Exos destroyed the microvascular structure of keloid tissue, resulting in a decrease in $CD31^+$ and $CD34^+$ blood vessels.[84] Similarly, BMSCs exosomes containing miR16 have been reported to inhibit tumor progression and angiogenesis by downregulating VEGF expression in breast cancer.[69] Furthermore, BMSCs exosome-derived miR-100 can also inhibit the angiogenesis of breast cancer by down-regulating VEGF expression through the mTOR/HIF-1α signaling.[70]

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In addition to suppressing angiogenesis by downregulating VEGF expression, studies have also found that MSCs-Exos could activate the extracellular regulated kinase 1/2 (ERK1/2) signaling, hence increasing the expression of VEGF and ultimately promoting tumor angiogenesis.[90] The above studies demonstrated the critical involvement of stem cell exosomes in angiogenesis. Given the complex effects of stem cell exosomes on angiogenesis, more research is necessary to clarify their precise mechanism involved.

Anti-Inflammation

Increased inflammation during the wound healing process may lead to aberrant scar formation, resulting in several atypical phenotypes including keloids and hypertrophic scars.[91] Macrophages, mast cells, and regulatory T cells participate in the process of scar formation.[92–95] Research indicates that MSCs-Exos possess immunomodulatory effects and reduce inflammatory responses via inhibiting immune cell function and inflammatory factor generation.[96] Specifically, Sun et al discovered that MSCs-Exos exerted anti-inflammatory effects by inducing regulatory T cell expansion and M2 macrophage polarization.[97] The study by Shahir et al exhibited that MSCs-Exos could alleviate DC-induced immunological responses and attenuate bone marrow DCs maturation.[98] Del Fattore et al found that BMSCs exosomes inhibited the proliferation of $CD4^+$ T cells and triggered their apoptosis.[99] Furthermore, Harrell et al treated microglial cells with MSCs-Exos, boosting the synthesis of anti-inflammatory cytokines (TGF-β and IL-10) while inhibiting the release of inflammatory cytokines (IL-1β and TNF-α) production.[96] The findings indicated that stem cell exosomes exerted anti-inflammatory properties through converting pro-inflammatory immune cells ($CD4^+$ T cells, M1 macrophages, and DCs,) into anti-inflammatory regulatory T cells, M2 macrophages, and tolerogenic DCs.

EMT Inhibition

EMT is a cellular process whereby epithelial cells undergo a phenotype transition to a mesenchymal state, hence promoting their invasive capacity. EMT contributes to the formation of keloids and hypertrophic scars.[100,101] Many studies have demonstrated that MSCs-Exos can improve EMT. For example, Li et al found that MSCs-Exos rich in miR-466f-3p reversed radiation-induced EMT by inhibiting the AKT/GSK3β signaling through c-MET targeting.[74] Li et al used HucMSCs-derived exosomes enriched with miR-15a-5p to target and downregulate CHEK1, ultimately inhibiting EMT in cholangiocarcinoma.[75] Jahangiri et al demonstrated that MSCs-exosomes significantly downregulated EMT of colorectal cancer cells through miR-100/mTOR/miR-143 signaling.[76] Furthermore, BMSCs-Exos enriched with miR-16-5p can restrain EMT of breast cancer cells.[102] Although most studies have found that MSCs inhibit EMT by targeting various signaling pathways, some research has demonstrated that MSCs-Exos may enhance EMT. For example, Shi et al revealed that BMSCs-Exos facilitated the EMT of nasopharyngeal cancer cells.[103] What's more, Zhou et al revealed that HucMSCs induce EMT through activating the ERK signaling, thereby promoting breast cancer progression and metastasis.[104] In summary, MSCs-Exos may play complex roles in EMT, with their specific roles in scar formation and development requiring further investigation.

Mesenchymal stem cells have multiple sources, and different sources can affect wound healing through different pathways or mechanisms (Table 2). To sum up, differences in MSC sources, exosome isolation methods, and wound

Table 2 Effects of Different Sources of MSCs-Exos on Wound Healing

Exos Source	Function and Mechanism	Reference
ADSCs	Increase collagen I and III generation in the early phase, and suppress collagen synthesis in the later phase to accelerate wound healing	[105]
HucMSCs	Enhance the expression of collagen I, III, and elastin mRNAs	[106]
ASCs	Regulate inflammation, suppress fibrotic remodeling, increase angiogenesis, and promote re-epithelialization of skin appendages,	[107]
hAECs	Induce MMP-1 expression to decrease ECM accumulation	[108]
BMSCs	Promote wound healing, decrease myofibroblasts deposition and scar formation	[109]

models can affect wound healing outcomes. Therefore, it is essential to choose the appropriate administration strategy and source of MSCs for different types of wounds.

Engineered MSCs-Exos

As previously mentioned, although MSCs-Exos positively affect scar formation inhibition, naturally produced exosomes have limitations that may restrict their therapeutic benefit, including impurity, limited yield, low drug delivery efficiency, and lack of targeting. Engineered exosomes are potential exosomes that have been loaded, modified, or edited to promote wound healing and prevent scar formation. For one thing, the engineering of exosomes can enhance their biological activity, purity, and yield. For another, engineered exosomes can carry various molecules, including drugs, growth factors, and cytokines, to improve wound healing by targeting specific pathways. Based on this, this section mainly reviews the methods for preparing engineered exosomes and their uses in scarless wound healing.

Preparation of Engineered MSCs-Exos

To facilitate the effective utilization of MSCs-Exos in scarless wound healing, researchers implemented bioengineering technology to improve their loading efficiency, targeting, and stability. MSCs-Exos can be designed into engineered exosomes with specific functions through parental cell-based and direct exosome engineering (Figure 4).[110] The stability

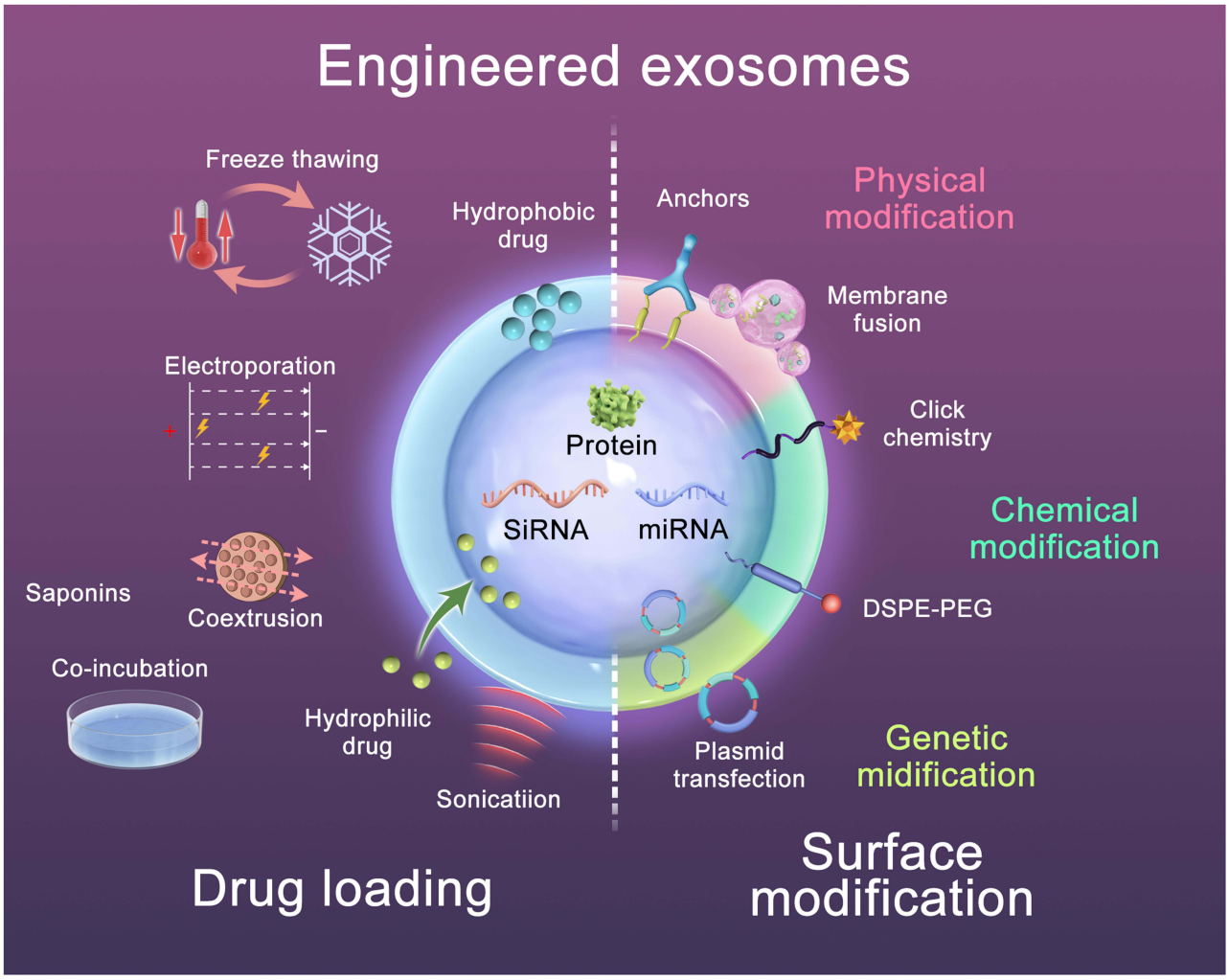

Figure 4 Schematic diagram of exosome engineering methods, including drug loading and surface modification.

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and drug loading efficiency of engineered exosomes vary according on the approach employed. The application examples of engineered exosomes obtained through various approaches in recent years are list in Table 3.

Direct Exosome Engineering

Exosomes frequently serve as carriers, enabling the direct introduction of target substrates into them via physical, chemical, or biochemical methods.

Biochemical Methods

The biochemical methods for exosome modification are highly effective, rapid, and straightforward. The biochemical methods mainly encompass direct co-incubation, saponin, membrane fusion, and click chemistry. Specifically, certain RNAs and small-molecule pharmaceuticals were integrated into exosomes through direct co-incubation, where they interacted with membrane lipid bilayers.[121] Due to drug hydrophobicity and gradient concentration, this approach has low loading efficiency.[122] What's more, studies have confirmed that the surfactant molecule saponin enhances loading efficiency by increasing membrane permeability.[123,124] For instance, saponin treatment increased catalase loading 11 times over passive incubation.[125] Nonetheless, saponins are acknowledged as hazardous agents that might cause hemolysis in vivo. Hence, saponins concentration must be precisely controlled, and exosomes need to be thoroughly washed following incubation. Direct modification through membrane fusion with target molecule-containing liposomes is another approach. For instance, Sato et al fused liposome bilayers generated by thin-film hydration and exosomes from macrophages made by the freeze-thaw method for the first time.[126] This strategy improves the characteristics and stability of exosomes while simultaneously diminishing immunogenicity, hence combining the benefits of two carriers in one drug carrier formulation.

Table 3 Representative Examples of Engineered Exos Preparation Methods and Applications

Producing Method	Exos Source	Cargos	Disease Model	Application	Reference
Lipofection	ADSCs	miR-29a	Kunming male mouse scald skin model	Scar formation inhibition	[66]
Electroporation	ADSCs	miR-21-5p	SD diabetic rat cutaneous wound model	Wound healing	[111]
Electroporation	Milk	miR-31-5p	BALB/c diabetic mouse cutaneous wound model	Wound healing	[112]
Lentiviral transfection	HEK293	miR-31-5p	SD diabetic rat cutaneous wound model	Diabetic wound healing	[113]
Lipofection	BMSCs	HOTAIR (lncRNA)	SD diabetic rat cutaneous wound model	Wound healing	[114]
Lipofection	ADSCs	Nrf2	SD diabetic rat cutaneous wound model	Diabetic foot ulcers treatment	[115]
Pretreatment (Atorvastatin)	BMSCs	-	SD diabetic rat cutaneous wound model	Diabetic skin defects treatment	[116]
Pretreatment (Hypoxia)	ADSCs	-	BALB/c diabetic nude mouse cutaneous wound	Diabetic wound healing	[71]
Pretreatment (Fe_3O_4+static magnetic field)	BMSCs	-	Rat critical-sized calvarial defect model	Bone regeneration	[117]
Lentiviral transfection	BMSCs	TSG-6	C57BL/6J mouse full-thickness cutaneous wound model	Scar formation inhibition	[118]
Co-incubation	EL-4	Curcumin	C57BL/6J mouse septic shock model	Septic shock treatment	[119]
Click chemistry	CDCs	Cardiac homing peptide	SD rat ischemia/reperfusion model	Myocardial damage repair	[120]

Chemical Methods

Chemical methods are a common method for exosome modification, which enables targeted drug delivery by coupling functional ligands to exosome surfaces. Click chemistry, also known as bioconjugation, is an efficient chemical conjugation approach for joining a selected biomolecule to a specified substrate. Specifically, copper-catalyzed azide-alkyne cycloaddition (CuAAC) bio-symmetrically conjugates exosomal alkyl-tagged proteins to azide-containing compounds. For instance, Jia et al conjugated the glioma-targeting peptide sequence RGERPPR (RGE) to exosomes using an orthogonal click chemistry method, after cyclizing it with sulfonyl azide.[127] This conjugation reactions does not alter the structure of exosomes, preserving their dimensions.[128] In summary, cell-type targeting specificity can be determined by chemical modification exosome surface, hence mitigating off-target effects. Nevertheless, this approach may lead to surface protein inactivation or exosome aggregation.[129] Additionally, the pressure, salt concentration, and temperature employed can lead to membrane rupture, excessive osmotic pressure, or surface protein denaturation.

Physical Methods

Physical methods mainly encompass sonication, electroporation, extrusion, and freeze-thaw cycles. Sonication is a common-used method for exosome engineering. Specifically, a homogenizer probe is used to sonicate a mixture of drugs and purified exosomes.[130] Sonication generates mechanical shear force, which causes membrane distortion in exosomes, allowing medicines to penetrate their core. The excellent loading efficiency and operational simplicity of this sonication method make it a popular choice. For instance, exosomes extracted from bovine milk that were loaded with PTX or 5-FU using sonication showed a greater drug loading efficiency than those that were treated with Triton X-100 and incubated.[131] Kim et al found that the sonication reshaping the exosomal membrane, thereby enhancing loading efficiency and prolonging drug release time.[132] In addition, Sun et al found that tissue-specific and responsive mRNA can be more effectively delivered via exosomes with the use of sonication, significantly boosting therapy effectiveness while minimizing off-target effects.[133] Nonetheless, sonication may cause exosomal aggregation and perhaps impair their activity, hence requiring rigorous instrument specifications. Additionally, sonication has the potential to compromise the structural integrity of exosomal plasma membranes, leading to drug leakage and inadequate drug loading.

Electroporation is promise for large compounds that exosomes cannot encapsulate. By temporarily perforating the exosome membrane and disrupting the phospholipid bilayer with an electrical field, electroporation makes it possible to load exosomes with nucleotides and chemotherapeutics.[130] For instance, Lv et al encapsulated miR-21-5p into ADSCs-Exos by electroporation, demonstrating significant efficacy in wound healing by promoting collagen remodeling, angiogenesis, and re-epithelialization.[111] Yan et al showed that milk-derived exosomes loaded with miR-31-5p mimic may promote angiogenesis in vivo, which could speed up wound healing (Figure 5).[112] Nevertheless, the loading efficiency may be overestimated due to the potential for siRNA aggregation to be induced by electroporation.[134] In addition, the efficacy of electroporation is affected by the concentration of exosomes and drugs, as well as the electroporation parameters. For instance, Lennaárd et al demonstrated that in a PBS solution containing 400 mM sucrose, electroporating 1×10^{11} exosomes at a ratio of 1 mM: 5×10^{11} with a 950 V and 50 μF electric pulse, resulted in a 20% enhancement in exosome recovery and an 18% increase in loading efficiency compared to the original protocol.[135] While electroporation has obvious advantages for difficult-to-load drugs and nucleotides, the high-voltage pulses may destroy membrane integrity and protein structure, leading to exosome aggregation and consequently reduced loading efficiency.

Another approach that makes use of severe mechanical force to load exogenous cargos into exosomes is extrusion. Unlike electroporation, extrusion disrupt the exosome membrane, which vigorously mixes the drug with the exosomes.[130] Hence, the high drug loading is further improved by the extrusion approach.[136] For example, a study encapsulated the GLP-1 receptor agonist liraglutide into milk-derived exosomes using six drug loading approaches- electroporation, saponin-assisted, freeze-thaw cycle, extrusion, sonication, and incubation.[137] The findings indicated that the liraglutide exosomes obtained by extrusion has a drug loading capacity 2.45 times higher than those obtained by direct co-incubation. What's more, Haney et al integrated catalase into exosomes by sonication, room temperature incubation, extrusion, saponin infiltration, and freeze-thaw cycles methods.[138] The results revealed that the extrusion method prompted exosome reorganization, resulting in enhanced loading efficiency and sustained release of catalase, as well

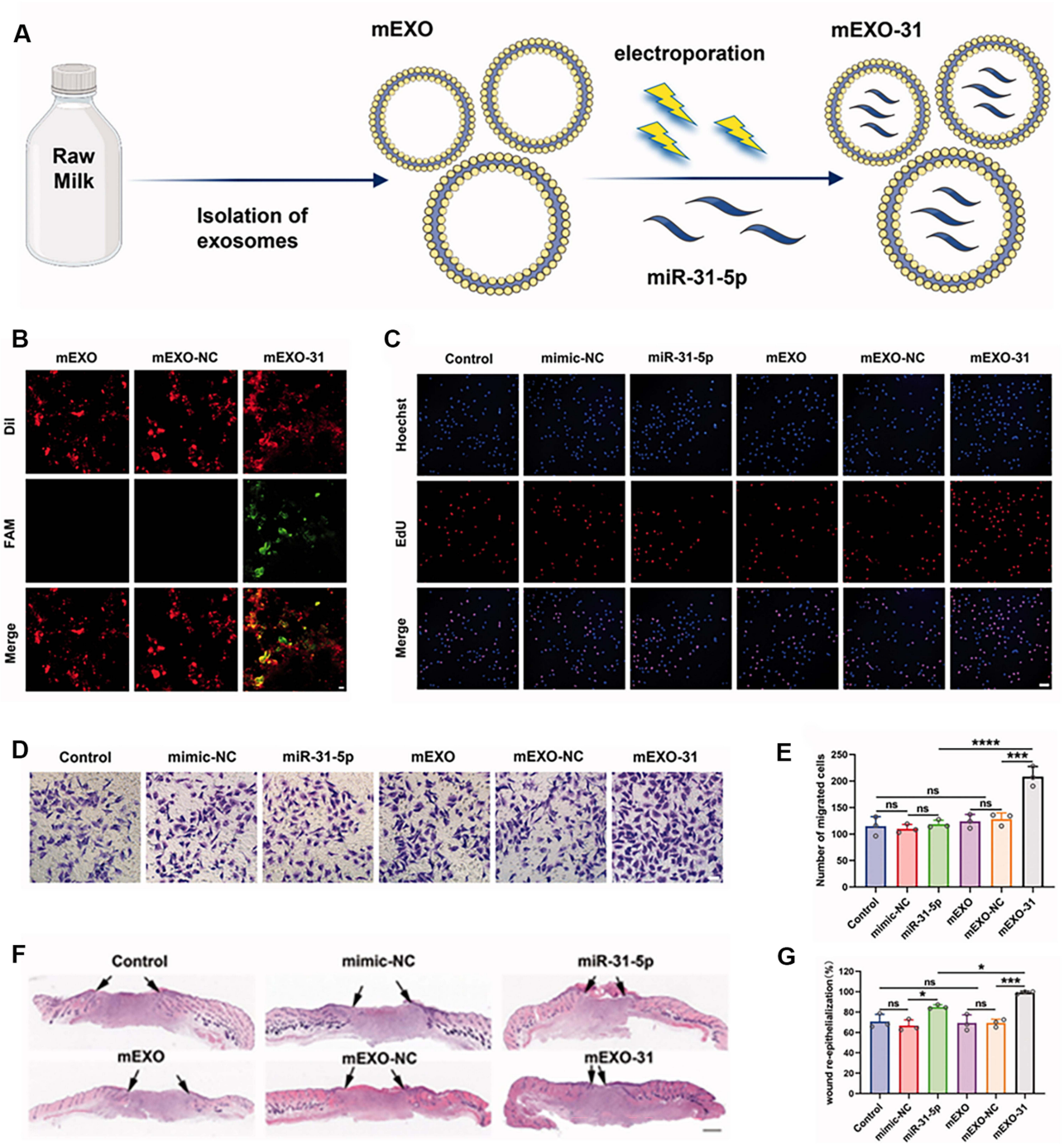

Figure 5 (**A**) Schematic image of miR-31-5p-loaded exosomes (mEXO-31) preparation. (**B**) Confocal photographs exhibited successful construction of mEXO-31. Scar bar = 10 μm. (**C**) Representative confocal images of HUVEC cells stained with EdU. Scar bar = 50 μm. (**D**) Images of transwell assay and (**E**) corresponding migrated contents. Scar bar = 50 μm. (**F**) Representative images of HE staining after different treatments on day 15 and (**G**) corresponding re-epithelialization rates. The single-headed arrows indicate the un-epithelialized areas. ns: no significant, *P < 0.05, ***P < 0.001, ****P < 0.0001. Reproduced with permission ref.[112] Copyright 2022, Taylor & Francis Group.

as preventing protease degradation. According to previous studies, the vesicle protein composition, delivery activity, and exosome integrity are all negatively affected by the extrusion process.[139,140]

Freeze-thaw cycling is a physicochemical procedure that involves mixing exosomes with medications, freezing them at −80°C or in liquid nitrogen, and then thawing them at ambient temperature. Following several freeze-thaw cycles, exosomes' minor lipid bilayer damage allowed therapeutic agents to diffuse into them.[139] More importantly, the bioactive

substances are rarely damaged by this gentle, easy-to-use approach. A thorough study by Li et al examined how drug loading approaches and physicochemical features including lipophilicity and molecular weight affect milk-derived exosome drug loading performance.[141] The result revealed that sonication method achieved the highest loading efficacy of 5-FU (37.65%), followed by a freeze-thaw cycle (35.21%). Notably, the freeze-thaw cycle method has low capture efficiency and may lead to exosome aggregation.

Parent Cell-Based Exosome Engineering

The goal of parental cell-based exosome engineering is to generate specifically tagged exosomes or to increase exosome yield while maintaining structural integrity. The genetic modification of parental cells to alter donor cells by integrating the desired target coding sequence through lentivirus or specific mRNA, followed by collection of exosomes with the target payload, is a convenient and reliable method.[142] For example, Huang et al used miR-31-5p lentiviral vector to transfect parental cells, producing exosomes carrying miR-31-5p for diabetic wound healing via RNA interference (RNAi) therapy.[113] To obtain MSCs-Exos loaded with long noncoding RNA HOTAIR, Born et al transfected MSCs with overexpressed HOTAIR. The findings indicated that Exos-mediated HOTAIR delivery significantly promoted wound healing.[114] What' more, Li et al demonstrated that exosomes extracted from Nrf2-overexpressing ADSCs could reduce inflammatory levels, enhance growth factor expression, and promote granulation tissue formation.[115] In summary, although modifying parental cells through genetic engineering to obtain exosomes rich in mRNA and proteins can promote wound healing, this approach possesses many drawbacks including fluctuating transfection efficacy and unstable gene expression.

In addition to genetic engineering, another way for modifying the cargo in exosomes is to incubate donor cells with desired molecules or change their culture environment. This approach emphasizes the preconditioning of parental cells, which primarily includes chemical agents, cytokines, magnetic fields, and hypoxic.[143] For instance, atorvastatin-pretreated MSCs promote angiogenesis via the AKT/eNOS signaling, which speeds up the healing of diabetic wounds.[116] By activating the PI3K/Akt pathway, exosomes produced by ADSCs grown in a hypoxic environment hasten the healing of wounds.[71] Furthermore, Wu et al successfully used magnetic nanoparticles and static magnetic field treatment in in vivo experiment to overexpress miR-1260a in BMSCs-Exos, thereby promoting bone regeneration and angiogenesis.[117] This method is simpler than genetic engineering, but it has issues with cytotoxicity and poor loading efficiency, and needs to be characterized before use.

To sum up, MSCs-Exos can be designed to serve specific functions as engineered exosomes through exosome engineering methods such as incubation, electroporation, ultrasound, and extrusion. Each of these methods has its own advantages and limitations (Table 4). Except for incubation, electroporation, extrusion, and ultrasound treatments all have the limitation of potentially damaging the membrane integrity of the exosomes. When choosing an exosome engineering method, first determine whether it involves internal loading or surface modification. For surface modification, physical modification is preferred for liposomes or cationic liposomes, while chemical modification is preferred for targeting peptides or nanobodies. For internal loading, incubation, sonication, and electroporation are commonly used methods. The incubation process is relatively simple, electroporation saves time, and sonication has a high loading efficiency. The specific choice can be determined based on the laboratory equipment available and the desired loading outcome.

Engineered MSCs-Exos in Scarless Wound Healing

In the previous section, we provided an overview of the preparation methods of engineered exosomes. Herein, we will discuss the application of engineered MSCs-Exos in scarless wound healing.

Researches have demonstrated that chronic inflammation and myofibroblast aggregation may result in pathological scar thickening on the wound surface, while the application of engineered MSCs-Exos can minimize scar formation through suppressing chronic inflammation and myofibroblast aggregation.[91,144] For instance, Fang et al confirmed that microRNAs (miR-23a, miR-21, miR-125b, and miR-145) in MSCs-Exos inhibited fibroblast and myofibroblast differentiation and decreased scar formation by targeting the TGF-β/Smad2 signaling using high-throughput RNA sequencing and functional analysis.[87] Yuan et al demonstrated that miR-29a overexpression in ADSCs-Exos suppressed post-burn scar hyperplasia via targeting TGF-β2/Smad3 signaling.[66] Notably, engineered MSCs-Exos can also prevent scar

Table 4 Advantages and Disadvantages of Engineered Exos Preparation Methods

Producing Method	Cargos	Advantages	Disadvantages	Scalability
Co-incubation	Hydrophilic and hydrophobic drugs, miRNA, and protein	Convenient, exosome membrane integrity, mild reaction condition, and enhanced drug solubility	Low loading efficiency, limited application, and potentially cytotoxic	Easily scalable
Electroporation	Drugs, miRNA, and dextran	Timesaving, able to incorporate large compounds, and enhanced loading efficiency	Exosome aggregation, size-dependent, and damage membrane structure integrity	Easily scalable
Saponin	Drugs and protein	Enhanced loading efficiency	Cytotoxic	Uncertain
Sonication	Drugs, miRNA, protein, and nanoparticles	Convenient and high loading efficiency	Exosome aggregation, function alternation, and damage membrane structure integrity	Easily scalable
Extrusion	Protein and porphyrins	High encapsulation rate	Damage membrane structure integrity	Easily scalable
Freeze-thaw cycle	Drugs and protein	Rapid loading, mild reaction condition, and easy to operate	Exosome aggregation and low encapsulation rate	Easily scalable
Chemical modification	Targeting peptide or nanobodies	High specificity and fast reaction time	Needs impurity removal and high technical requirements	Easily scalable
Physical modification	Lipofectamine and pullulan	Easy to operate	Low loading rate	Uncertain
Transfection	LncRNA and miRNA	Wide applications	Transfection rate variable	Uncertain

formation through decreasing the expression of inflammatory factors. The study by Wgealla et al demonstrated that human amniotic fluid stem cell exosomes reduced the generation of inflammatory-associated cytokines through miR-146a-5p, thereby reducing scar formation.[145] What's more, Jiang et al infected MSCs with lentivirus to obtain TNF-stimulated gene-6 (TSG-6)-modified MSCs-Exos. The results indicated that the engineered MSCs-Exos decreased inflammation of pathological scars through lowering levels of IL-1β, MCP-1, IL-6 and TNF-α in scar tissue, ultimately decreasing scar formation.[118] In summary, engineered MSCs-Exos represent a promising strategy for boosting biological activity and repairing damage while decreasing scar formation. However, it is necessary to note that the improvements in wound healing or scarring are modest or context-dependent.

Applications of Hydrogels and Exosomes Composites in Scarless Wound Healing

Although engineered MSCs-Exos are expected to boost wound healing and prevent scarring. Because of the high clearance rate and short half-life, using exosomes in scarless wound healing remains challenging. In addition, the activity and functionality of free exosomes are negatively impacted since wound healing often takes a long time. Hydrogels, characterized by their exceptional hydrophilic and biocompatibility, providing abundant storage space for exosomes while preserving bio-stability. The encapsulated exosomes are gradually released when the hydrogels degrade in wound microenvironments to exert anti-scarring effects.

Hydrogels can be categorized according to their source (natural versus synthetic), cross-linking mechanism (chemical versus physical), polymer charge (anionic, cationic, neutral), chemical structure (copolymer versus homo-polymer; miscellaneous, protein/peptide, polysaccharide), and biodegradability. With an emphasis on the utilization of Exos-loaded hydrogels in scarless wound healing, this section will investigate the most important aspects of hydrogels from the perspectives of gelation mechanism, Exos loading, and release (Figure 6).

Mechanism of Gelation

The gelation mechanism is crucial for regulating the microstructure of hydrogel carriers. To date, chemical and physical crosslinking are the primary mechanisms of gelation. Physical crosslinking typically relies on hydrophobic interactions,

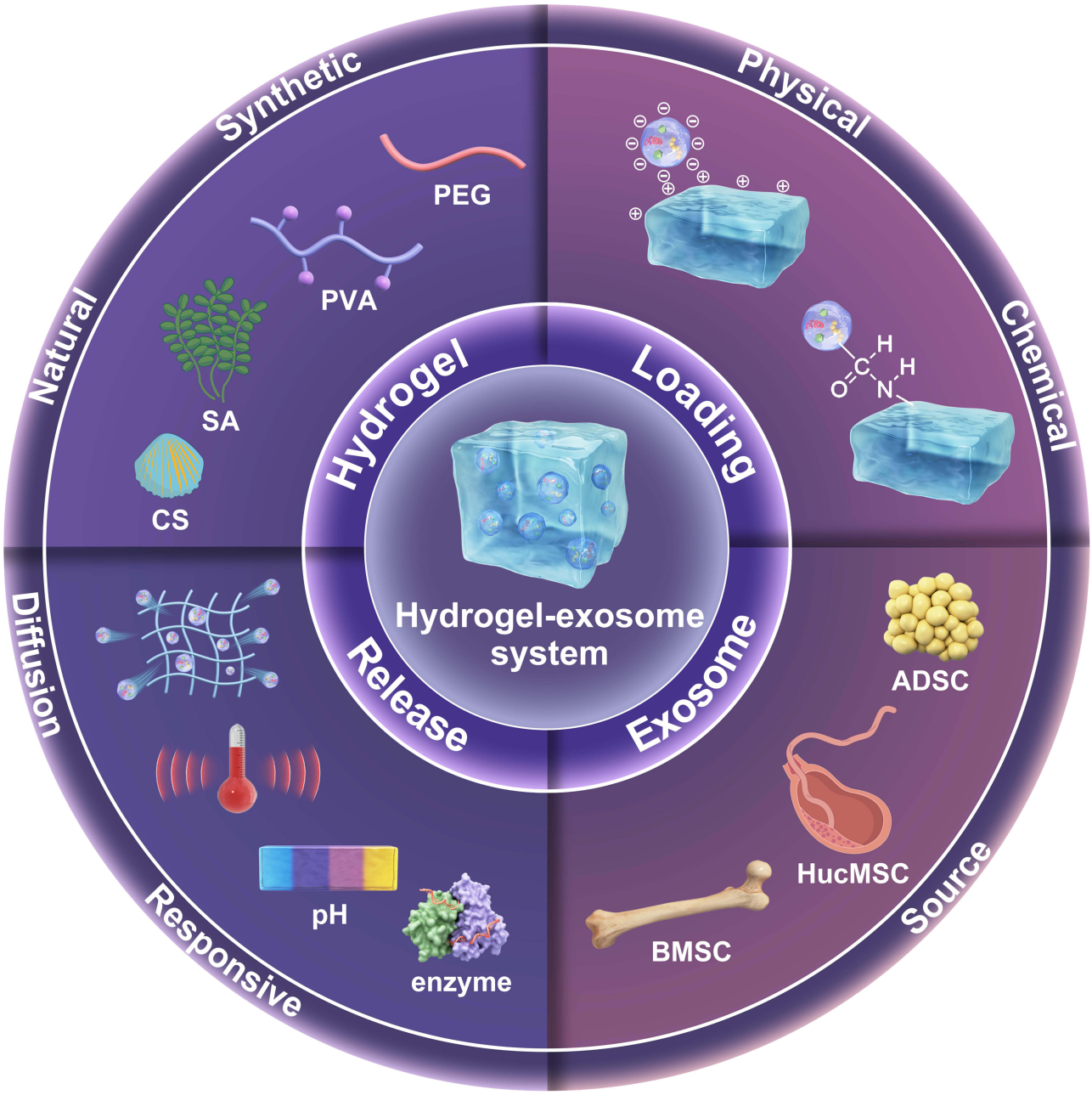

Figure 6 Schematic diagram of the Exos-loaded hydrogels for scarless wound healing.

hydrogen bonding, polymer and ionic interactions, and crystallization to form a weaker gel structure.[146] Physical crosslinking can respond to environmental factors such as temperature to achieve sol-gel phase transition. For instance, polysaccharide hydrogels embedded with Exos, including β-glycerophosphate,[147] pluronic F127,[148] poly (N-isopropylacrylamide),[149] poly (N-vinyl caprolactam),[150] poly (D, L-lactide-co-glycolide)-b-poly (ethylene glycol)-b-poly (D, L-lactide-co-glycolide),[151] methylcellulose,[152] and (hydroxypropyl) methylcellulose[153] typically undergo sol-gel phase transitions at relatively low critical solution temperatures. Additionally, certain polymers are able to undergo chemical modification with certain functional groups to form thermo-responsive physically cross-linked hydrogels, such as N-isopropylacrylamide and N-vinylcaprolactam.[154]

Different from physical crosslinking, chemical crosslinking occurs when covalent bonds are formed between polymer's functional groups and other active groups within the system. Chemical crosslinking enables on-demand gel

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structures through enzyme-triggered reactions, photo-induced reactions, as well as a variety of click reactions and bioorthogonal reactions.[155] For example, modification of the hydrogels with photoactivatable functional groups such as o-nitrobenzyl alcohol, thiol, acrylate, vinyl, and maleimide in the presence of a photoinitiator, resulting in photo-induced cross-linking at specific wavelengths.[156] For instance, Xu et al designed light-triggered o-nitrobenzyl alcohol-modified hydrogels loaded with Exos from stem cells to accelerate wound epithelialization.[157] To develop horseradish catalase-triggered functional hydrogels, Feng et al modified KGM and Hep polysaccharide polymers with tyramine groups. The findings demonstrated that the hydrogel successfully facilitated angiogenesis in vivo without adding any exogenous protein.[158] In addition, Shen et al constructed a polyethylene glycol diacrylate/thiolated alginate bilayer hydrogel via thiol-ene click chemistry. The bilayer hydrogel greatly boosted wound healing and minimized scar formation.[159] Furthermore, Nagahama et al constructed tissue-crosslinked hydrogels TxGels through bioorthogonal crosslinking of alkyne-modified polymers and azide-modified cells. The bioactive hydrogel could create three-dimensional cellular assemblies of different cells and was suitable for organ-chips techniques.[160] The aforementioned are various instances of chemical cross-linking methods employed in the literature to develop Exos-loaded hydrogel systems.

To prevent adverse impacts on the stability of the Exos or their cargos, it is essential to note that the crosslinking approach for the Exos-embedded hydrogels needs to be carefully chosen. Specifically, the functionality and integrity of the Exos membrane may be impacted by elevated temperature, free radicals, and metal ions. Consequently, we think that future study should concentrate on ensuring that the crosslinking approach is compatible with the hydrogel-embedded Exos and their cargos.

Hydrogel Loading of Exos

Since the initial loading amount of cargo might influence the release of hydrogel systems,[161] it is imperative to explore approaches for precisely controlling cargo loading. The emergence of 3D printing and microfluidics may provide methods for precisely loading cargo into hydrogels.[162] Typically, hydrogel loading of Exos is accomplished by dispersing Exos in hydrogel-forming polymers, cross-linkers, or their mixture prior to cross-linking.

The hydrogel loading of Exos is influenced by the hydrogel network mesh size, along with the Exos-polymer interaction. Hydrogel mesh size depends on the gel ionic strength, pH and cross-linking degree, as well as swelling-controlling environmental factors including temperature. It seems unlikely to determine an optimal mesh size range for Exos-loaded hydrogels that is appropriate for all vesicles and applications. Nonetheless, the emergence of machine learning methodologies and big data analytics may clarify the ideal range of release profiles and vesicle characteristics thereby providing mathematical models to predict the values of pore size-controlling parameters (eg, cross-linker concentration).

Physical and covalent interactions between Exos and polymers are another parameter that affect hydrogels' capacity to encapsulate Exos. For one thing, hydrogels composed of charged polymers exhibit a reduced ability to bind Exos with like charges. For another, both covalent and non-covalent bonds formed between polymers and Exos enhanced the hydrogel system's ability to bind Exos. For instance, Exos with negative charges can be loaded more efficiently into hydrogels that are positively charged, such as chitosan. Nevertheless, Exos-polymer electrostatic interaction is merely one factor influencing the loading capacity. Notably, covalently attaching Exos to hydrogel-forming polymers is an understudied approach to improve Exos loading capacity and continuous release. An interesting example of such research was reported by Zou et al, who anchored epoxy-grafted Exos to thiohyaluronic acid.[163] Although decreased Exos activity was not reported in this case, the most important concern remains whether Exos retain their functionality following chemical modification.

Hydrogel Release of Exos

Hydrogel carriers provide an ideal platform for developing controlled-release drug delivery systems. Given that Exos hydrogels applied to the skin affect the skin wound healing process,[164] it is particularly crucial to study the release kinetics of Exos. The lipid composition and particle size of Exos determine their membrane stiffness and interaction with the hydrogel, ultimately effecting Exos release from hydrogel carriers.[165,166] Moreover, hydrogel payload release is

governed directly by polymeric network mesh size. Hydrogel release patterns are characterized by cargo diffusion, polymeric network deformation, swelling, and degradation, and any external or internal factors affecting these processes are able to exploited to develop responsive release systems.[167,168] Temperature,[169] ionic strength,[170] specific enzymes,[171] oxidation state,[172] and external stimuli including electromagnetic waves,[173] ultrasound,[174] electric current,[175] and magnetic fields[176] are all able to designed to facilitate the release of Exos from hydrogels.

For example, the photothermal effect to destroy chitosan networks,[177] an acidic microenvironment to decompose thiolated chitosan,[178] and the generation of ROS to destroy boronic esterified dextran[179] have all been employed to release drugs from polysaccharide-based hydrogels. Shen et al constructed a bilayer hydrogel (BSSPD) composed of PEG diacrylate and different thiolated alginate loaded with sEVs, with the goal of addressing wound healing issues at many phases. In vitro and in vivo assays also confirmed that the sequential release of sEVs in the BSSPD facilitated wound healing while suppressing scar formation (Figure 7).[159] What's more, Wang et al developed a thermosensitive polysaccharide dressing (FEP) carrying ADSCs-derived exosomes. The Schiff base of the scaffold enables the pH-responsive continuous release of exosomes, which promotes wound healing. The FEP@exo scaffold dressing treatment resulted in minimal scar tissue and visible skin appendages, demonstrating that it can promote collagen deposition while both preventing scar formation and generating skin appendages.[180]

In dermal drug delivery, few studies have taken into account the fact that some parameters influencing Exos release from hydrogels also affect cargo release of Exos. Additionally, most studies have ignored the ratio of drug released as intact Exos to overall drug released.[156] Given that hydrogels can prevent the rapid clearance of the loaded exosomes, placing them at the wound site can concentrate the local dosage. To sum up, wound healing is a slow process, and the encapsulation of exosomes in hydrogels enables a slow and continuous release, providing moisture and suitable conditions for the proliferation and differentiation of cells at the wound site, thereby promoting wound healing and reducing scarring.[181]

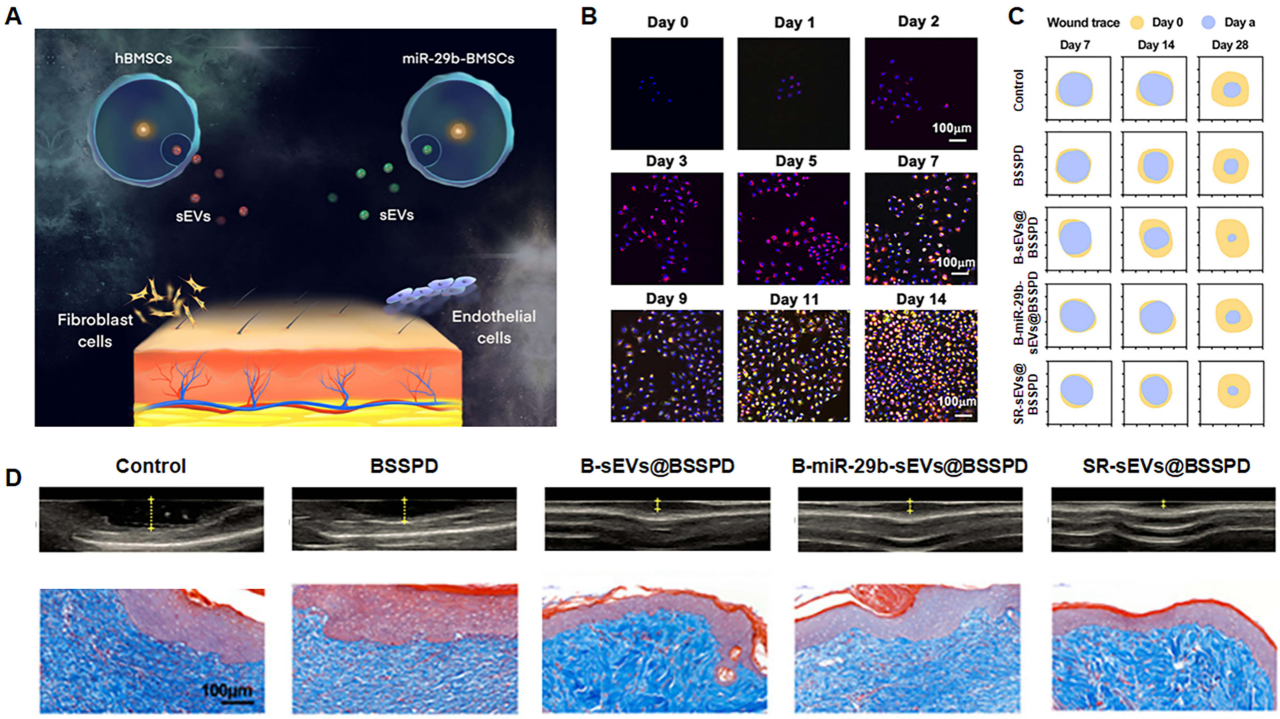

Figure 7 (**A**) Mechanism diagram of the bilayered hydrogel SR-sEVs@BSSPD for sequential release of sEVs. (**B**) Representative fluorescence images of sEVs with increasing immersion time. (**C**) Simulation plots of wound closures traces. (**D**) Ultrasonography and Masson staining in the wound bed after different treatments. The yellow bidirectional arrow represents the thickness of the scar. Reproduced with permission ref.[159] Copyright 2021, American Chemical Society.

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Applications of Exos-Based Hydrogels in Scarless Wound Healing

Both the early antioxidant, antimicrobial, and anti-inflammatory functions, along with the subsequent anti-scarring and angiogenesis conditions determine the overall wound healing condition.[182] Unfortunately, as mentioned above, neither engineered nor natural Exos are able to fully match scarless wound healing ‘s various needs. Therefore, combining two or more types of vesicles could be a promising approach for future wound care. For instance, Aijaz et al co-encapsulated insulin-secreting cells and MSCs in a hydrogel dressing to accelerate chronic wound healing while reducing or eliminating scar formation, paving the way for future dual-cell therapies.[183] In addition, Exos-based hydrogels incorporating antioxidant and antimicrobial agents can be used to heal infected wounds without scarring. For example, Shiekh et al developed an antioxidant hydrogel dressing OxOBand containing ADSCs-derived exosomes by employing an antioxidant polyurethane (PUAO) as a cryogel scaffold. The dressing kept the wound from getting infected and ulcerated while speeding up healing by promoting collagen deposition. This gave the wound a follicular and epidermal morphology akin to normal skin.[184] Qian et al introduced antibacterial AgNPs into CTS-SF/SA scaffolds to construct multifunctional exosome-based hydrogel dressings. CTS-SF/SA/Ag-Exo dressings demonstrated excellent antibacterial activity and wound healing effects, and were expected to provide the possibility of scar-free healing of clinical infected wounds.[185] Furthermore, Yang et al modified a macroporous hydrogel wound dressing that contained HucMSCs-derived exosomes with antimicrobial peptides to obtain HD-DP7/Exo. HD-DP7/Exo achieved the dual functions of antibacterial and scarless wound healing in vivo by shortening wound closure time and preventing collagen accumulation (Figure 8).[186]

To enhance the biological stability of Exos, natural polymers like alginate[142] and chitosan as well as synthetic polymers like Pluronic F-127[187–189] and polylactic acid have been used for Exos delivery. Among them, some synthetic polymers exhibit favorable thermo-sensitivity and can form gel-like substances that are compatible with complex wounds and better mimic ECM. Combining the aforementioned biomaterials with Exos to promote wound healing has achieved ideal results. Examples of wound healing applications of biomaterial hydrogels combined with Exos in recent years are list in Table 5.

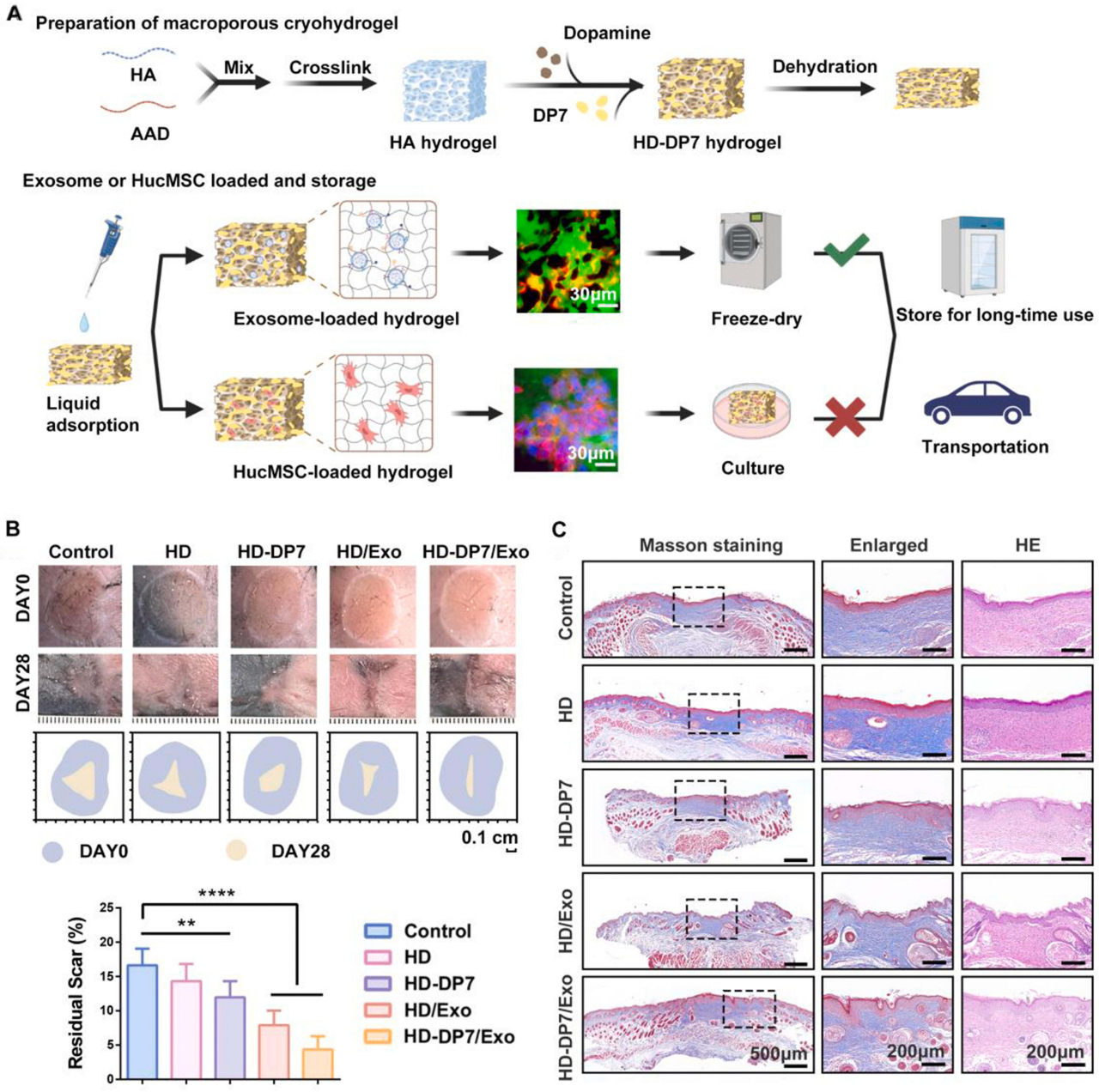
Although Exos combined with hydrogels have made some progress in wound healing, the targeted and sustained delivery of Exos through biological scaffolds alone remains challenging. In contrast, 3D bioprinting technology can well control the porosity while keeping scaffold mechanical and structural integrity, enabling long-term sustained delivery of Exos.[201] Up to now, 3D bioprinting technology has been used to induce neovascularization and promoting cartilage regeneration. For instance, Chen et al designed ECM/GelMA/exosome scaffolds for repairing cartilage via 3D printing. This scaffold has been proven to successfully cure mitochondrial dysfunction, promote migration, and exhibiting promising therapeutic effects for cartilage defect repair.[202] What’ more, the 3D-bioprinted constructs containing HUVECs-derived Exos developed by Maiullari et al enable in situ functional vasculature formation.[203] During the bioprinting process, increasing the cross-linker concentration can decrease the initial release rate of Exos while preserving their bioactivity.[23] However, physical or chemical interactions between biomaterials and Exos, together with residual cross-linker toxicity, will limit their further application. In addition, there is currently no research on exosome-loaded 3D-printed scaffolds for scarless wound healing, and the pros and cons remain to be evaluated. Moreover, studies have shown that with the continuous development of skin bioelectronics, conductive hydrogels used for personal therapy and health management are ideal candidates for exosome carriers and have also become one of the promising solutions for scar-free wound healing.[204–206] Last but not least, the aforementioned scarless healing studies are all based on animal models, which differ clearly from human clinical data, and this is also something that needs to be taken into consideration.

Challenges and Future Perspectives in Clinical Application of MSCs-Derived Exos

Although MSCs-Exos therapy is a promising cell-free therapeutic approach, it still faces some challenges. The first challenge is that current Exos production methods have low yield, purity, practicality and economic problems caused by the lack of standardized procedures for their purification, manufacture, and isolation. Therefore, stable and high-yield

Exos production methods are urgently needed to expand clinical applications of Exos.[207] The next challenge is that there is currently no effective evaluation protocol to evaluate the specific content of Exos, as Exos composition varies according to the source and culture conditions. The third challenge is that Exos therapy poses the risk of immunological rejection and toxicity. Currently, preclinical studies have not provided data regarding the carcinogenic potential of Exos or their molecular characteristics in vivo. Therefore, it is essential to conduct toxicological analysis and long-term health safety assessments of MSCs-Exos from different sources to confirm their biosafety. Up to now, only a small amount of Exos for wound repair have entered clinical trials. Table 6 summarizes Exos' clinical trials in wound healing, such as skin rejuvenation and burn wounds.

To safely and successfully integrate Exos-based therapy into wound healing clinical trials, MSCs-Exos isolation, generation, purification, identification, and preservation must be optimized. In addition, studying the biodistribution,



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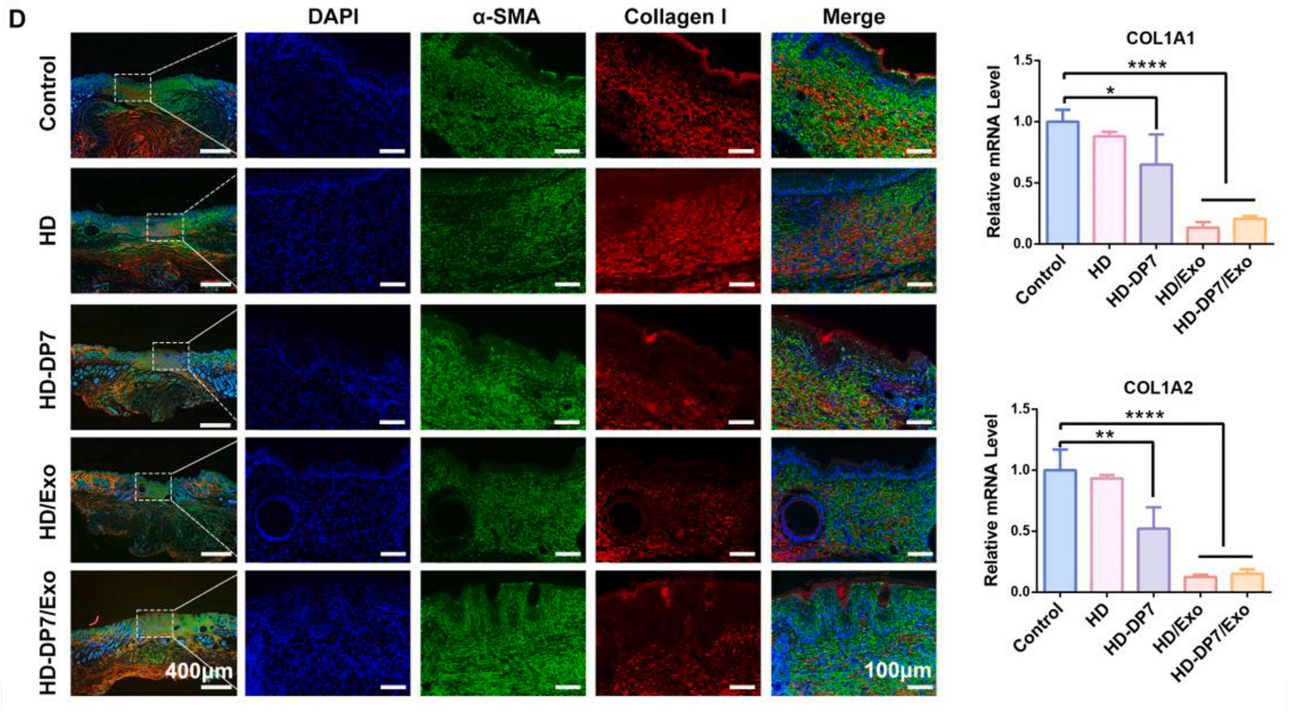

Figure 8 (**A**) Schematic diagram of the preparation of HucMSCs-Exo-loaded macroporous hydrogel HD-DP7/Exo. (**B**) Representative images of scar areas in mice after different treatments and the corresponding statistical results of residual scar areas. (**C**) Representative images of HE and Masson staining after different treatments. (**D**) Representative immunofluorescence staining images of α-SMA and type I collagen and the expression levels of COL1A1 and COL1A2 following treatment. Data are presented as the mean ± SD. *P < 0.05, **P < 0.01, ****P < 0.0001. Reproduced with permission ref.[186] Copyright 2024, Elsevier.

pharmacodynamics, and pharmacokinetics of Exos from different sources in vivo is also crucial, as is determining the optimal dosage and administration method.[14] Given that local administration remains the primary method of using Exos for wound repair, it is expected that clinical application can be achieved through developing scoring criteria for various wounds such as burns, infections, and scars, as well as selecting Exos biomaterials with corresponding effects. Furthermore, the research on the biological mechanisms of Exos should not only focus on signaling pathways, but

Table 5 Summary of MSCs-Exos Combined with Hydrogels Used in Wound Repair

Main Hydrogel-Forming Polymer	Other Formulation Components	Loaded Exos	Disease Model	Advantages	Disadvantages	Reference
Pluronic F127	-	HucMSCs-Exos	SD diabetic rat cutaneous wound model	Temperature sensitivity	Failed to elucidate the mechanism by which HucMSCs-Exos regulate angiogenesis	[187]
Carboxymethyl chitosan	Poloxamer 407, Genipin	HucMSCs-Exos	Mouse cutaneous wound model	Biodegradable, thermo- and pH-responsive release	Not mentioned	[190]
Carboxyethyl chitosan	Dialdehyde carboxymethyl cellulose	BMSCs-Exos	SD diabetic rat cutaneous wound model	Anti-inflammatory, antibacterial and angiogenesis	Failed to elucidate the mechanism by which BMSCs-Exos suppress inflammation	[191]

(*Continued*)

Table 5 (Continued).

Main Hydrogel-Forming Polymer	Other Formulation Components	Loaded Exos	Disease Model	Advantages	Disadvantages	Reference
Chitosan	-	SMSCs-Exos	SD diabetic rat cutaneous wound model	Promoting granulation tissue formation and angiogenesis	Failed to elucidate the mechanism by which SMSCs-Exos regulate angiogenesis	[192]
Chitosan	Glycerol	hEnSC-Exos	BALB/c mouse cutaneous wound model	Biodegradable	Not mentioned	[193]
Chitosan	Silk fibroin	GMSCs-Exos	Diabetic mouse cutaneous wound model	Hemostatic, antibacterial, biocompatible and biodegradable	Limitations of animal models and experiments	[194]
Chitosan	Silk fibroin, Ag NPs	HucMSCs-Exos	BALB/c male mouse infected cutaneous wound model	Broad-spectrum antimicrobial activity, promoting wound healing, retaining moisture and maintaining electrolyte balance	Failed to elucidate the mechanism by which promote nerve repair	[185]
Polyurethane	Calcium peroxide	ADSCs-Exos	Wistar diabetic rat infected cutaneous wound model	Preventing infection and ulceration, improving wound healing with improved re-epithelialization	Limitations of animal models and experiments	[184]
Hyaluronate	Dopamine, DP7	HucMSCs-Exos	C57BL/6J mouse deep second-degree burn infection model	Inhibiting bacterial growth and leading to scarless healing	Lack of good tensile properties	[186]
Hyaluronate (oxidized)	Pluronic F127, Poly-ε-lysine	ADMSCs-Exos	ICR male diabetic mouse cutaneous wound model	Antibacterial, thermo- and pH-responsive release	Limitations of animal models and experiments	[189]
Hyaluronate (oxidized)	Gelatin, Polydopamine NPs	HucMSCs-Exos	C57/BL/6 male mouse cutaneous wound model	Injectable, anti-inflammatory, biocompatible and radical neutralizing	Not mentioned	[195]
Hyaluronate (methacrylated)	Irgacure 2959	hMSCs-Exos	-	3D bioprinting patches, injectable and controlled release	Poor mechanical stability	[196]
Thiolated alginate	PEG diacrylate	BMSCs-Exos	SD rat cutaneous wound model	Sequential release of exos, achieving scarless wound healing	Not mentioned	[159]
Alginate	Calcium chloride	ADSCs-Exos	Wistar rat cutaneous wound model	Biocompatible, biodegradable, non-antigenicity and high absorbent	Lack of good tensile properties	[197]
Alginate	Silk fibroin, Calcium chloride	HBM-MSC-Exos	-	Highly absorbent, bacteriostatic and cell-adhesive	Separation acquisition is difficult	[198]
Alginate	PVA, Calcium chloride	HucMSCs-Exos	SD diabetic rat cutaneous wound model	Injectable, controlled release and biodegradable		[199]

(*Continued*)

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Table 5 (Continued).

Main Hydrogel-Forming Polymer	Other Formulation Components	Loaded Exos	Disease Model	Advantages	Disadvantages	Reference
Gelatin methacryloyl	Poly (lactide-co-propylene glycol-co-lactide) dimethacrylates	hMSCs-Exos	C57BL/6J male mouse cutaneous wound model	Controlled release and scarless wound healing	Not mentioned	[200]

Table 6 Clinical Trials of Exos in Wound Healing

Identifier	Condition or Disease	Exos Raw Materials	Recruitment Status	Phase
NCT04664738	Skin graft	Platelet	Active, not recruiting	Phase 1
NCT02565264	Intractable cutaneous wound ulcer	Plasma	Unknown	Early phase 1
NCT05078385	Second degree burn wounds	BMSCs	Completed	Phase 1
NCT04173650	Dystrophic epidermolysis bullosa	MSCs	Recruiting	Phase 1 Phase 2
NCT04134676	Chronic ulcer wounds	MSCs	Completed	Phase 1
NCT02138331	Diabetes mellitus type 1	MSCs	Unknown	Phase 2 Phase 3
NCT05243368	Cutaneous ulcers in diabetics	MSCs	Recruiting	Not applicable
NCT04652531	Ulcer venous	Autologous serum	Recruiting	Not applicable
NCT05813379	Skin rejuvenation	MSCs	Recruiting	Phase 1 Phase 2
NCT05243368	Diabetic foot	MSCs	Recruiting	Not applicable
NCT05475418	Wounds and injuries	Human adipose tissue	Completed	Not applicable

also involve cellular cascade reactions and deeper molecular biological mechanisms. Finally, to explore the mechanisms of wound repair, it is critical to identify and functionally study the contents of Exos. The study of Exos' therapy efficacy is expected to further promote their clinical application.

Conclusions and Future Direction

MSCs-Exos are increasingly favored in inhibiting scar formation during wound healing due to their excellent immunomodulatory and regenerative properties. However, MSCs-Exos have a short half-life and a high clearance rate in vivo, and their separation and purification are challenging. Combining exosomes with hydrogels can overcome their high clearance rate and poor biosafety. Nevertheless, there are currently few reports on the pharmacokinetics of Exos-loaded hydrogels. The development and precise evaluation of controlled-release systems under complex clinical conditions remain ongoing challenges.

In the foreseeable future, we should focus on the large-scale clinical production and application of MSCs-Exos-based materials. It is essential to improve the standard procedures for their production, separation, purification, and characterization, and to develop standardized protocols for combining MSCs-Exos with hydrogels for different wounds types, enhancing their market value while controlling costs, so that they can become a safe and effective wound healing therapy at the clinical level.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare no conflicts of interest in this work.

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