Chinese Chemical Letters 36 (2025) 109766

Contents lists available at ScienceDirect

Chinese Chemical Letters

journal homepage: www.elsevier.com/locate/cclet

Engineering strategies of biomaterial-assisted exosomes for skin wound repair: Latest advances and challenges

Yang Xu, Le Ma, Yang Wang, Chunmeng Shi*

Institute of Rocket Force Medicine, State Key Laboratory of Trauma and Chemical Poisoning, Third Military Medical University (Army Medical University), Chongqing 400038, China

ARTICLE INFO

Article history:
Received 29 January 2024
Revised 11 March 2024
Accepted 12 March 2024
Available online 13 March 2024

Keywords:
Exosomes
Biomaterials
Hydrogel
Delivery system
Wound healing

ABSTRACT

The treatment of skin wounds, especially chronic wounds, remains a critical clinical challenge and places a heavy burden on patients and healthcare systems. In recent years, the engineering strategy of using biomaterial-assisted exosomes has emerged as a powerful tool for skin repair. Compared to treatments such as debridement and regular dressing changes, the design of biomaterial-assisted exosomes not only maintains the bioactivity of exosomes at the wound site but also provides an appropriate microenvironment for the repair of complex tissues, thereby accelerating wound healing. This review systematically introduces the general characteristics of exosomes and their functions in skin wound healing, highlights recent advances in classification of natural exosomes and engineering methods which enriching their functions in intercellular communication. Then, various emerging and innovative approaches based on biomaterials delivery of exosomes are comprehensively discussed. The review seeks to bring an in-depth understanding of bioactive dressings based on exosomes therapeutic strategies, aiming to facilitate new clinical application value.

1. Introduction

The increasing number of patients with skin injury, especially chronic wounds such as pressure ulcer, vascular ulcers, diabetic foot ulcer (DFU) [1], will affect an estimated 20 to 60 million people worldwide by 2026, which will reach epidemic proportions, placing a heavy burden on patients and healthcare systems [2,3]. Chronic wounds are mainly impeded by bacterial infections, persistent inflammation, impaired angiogenesis, and high levels of reactive oxygen species (ROS) [4,5], which are difficult to heal and can eventually lead to serious consequences such as amputation and sepsis [6,7]. Traditionally, the clinical treatment of chronic wounds includes debridement, negative pressure treatment, regular dressing change and engineered skin, *etc*. [8]. However, the treatment involved lacks the ability to actively improve the wound microenvironment and guide the behavior of cells around the wound, which will not restore the normal physiological structure and function of the skin, so the repair effect is usually poor [6,9].

Recent studies have shown that the positive efficacy of stem cell therapy was largely due to the exosomes released by its paracrine action [10,11]. Once released from the cell surface, exosomes can interact with the extracellular matrix or initiate reactions within the microenvironment to promote cell proliferation, migration, and angiogenesis, using biological barrier crossing capabilities [12,13]. Due to the complicated local microenvironment of chronic wounds and the long healing time, free exosomes have certain limitations, such as short half-life, instability *in vivo*, and fast clearance rate, satisfactory results may not be achieved [14]. Therefore, accurate local delivery and sustained release of exosomes to target tissues is of great significance for chronic wound management, improving therapeutic performance and reducing side effects [15]. As a result, the design of biocompatible scaffolds that can maintain the function and continuous release of exosomes is crucial for exosomes-based wound healing therapies [16]. It can not only serve as a controlled release carrier for exosomes to maintain their biological activity in skin wounds, but also provide a suitable microenvironment for the repair of complex tissues to further accelerate wound healing, which is a promising skin regeneration strategy [17,18].

In recent years, promising applications of exosomes in tissue engineering have attracted tremendous attention, and some critical progress has been made, such as the central nervous systems, brain, bone, cartilage, heart, and endodontium. Besides, biomaterials have drawn growing attention not only as scaffolds for cell proliferation and structural support, but also as modulators to regulate

* Corresponding author.
E-mail address: shicm@sina.com (C. Shi).

https://doi.org/10.1016/j.cclet.2024.109766
1001-8417/

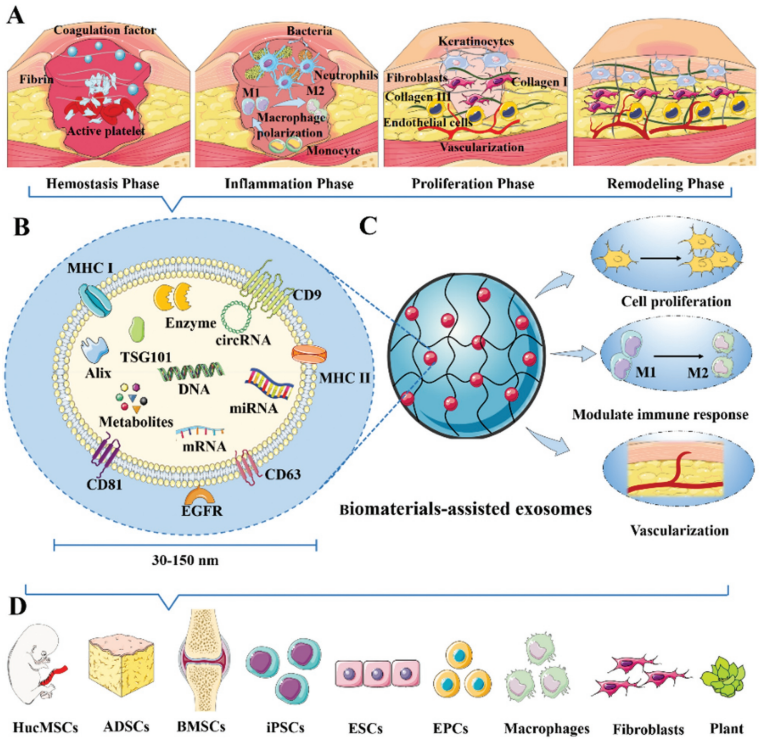

Fig. 1. Schematic overview of biomaterials-assisted exosomes in the skin wound repair. (A) The functions of exosomes in the skin wound healing process. (B) Elements of a typical exosome. (C) Biomaterials-assisted exosomes to achieve cell proliferation, modulation of immune response, and vascularization. (D) Exosomes from different cell sources.

cell/tissue behaviors and can further modulate a myriad of biological processes, from cell cycle, migration, proliferation and differentiation to neural conduction, muscle contraction, embryogenesis, and tissue regeneration [19–21]. To the best of our knowledge, many review articles have reported exosomes and biomaterials applying on the biomedical application, respectively, but few articles have discussed the application of the combined therapeutic effects of the two in skin wound healing. Considering the rapid growth of interest in this field, this review attempts to provide a comprehensive discussion of regenerative medicine engineering strategies based on macromolecular biomaterial-assisted exosomes in recent years. Firstly, we systematically summarized the biogenesis of exosomes and their biological regulatory functions in various phases of skin wound healing (Fig. 1A); Then, the exosomes of different cell origin and their engineering modification methods were concluded; Subsequently, we focused on the biomaterials-based delivery systems for maintaining exosomes bioactivity and therapeutic strategies for optimizing exosomes release (Figs. 1B and C); Finally, we figured out the relevant challenges and prospects. This review aims to inspire and encourage more researchers to further promote the development of biomaterial-assisted exosomes biomimetic strategies for skin wound healing, hoping to realize their clinical application value as soon as possible.

2. Biogenesis of exosomes and their functions in the wound healing process

Traditionally, extracellular vesicles (EVs) secreted by cells have been classified into apoptotic bodies, microvesicles and exosomes according to their unique biological mechanisms [22,23]. Apoptotic bodies are produced by the cell membrane to the outgoing bud during the process of apoptosis [24]. Microvesicles are also generated from the plasma membrane to outgoing buds but may be accompanied by apoptosis [25]. In contrast, exosomes formation involves four distinct stages: budding, endosome formation, fusion, and secretion [26]. At the beginning, the cell membrane invaginates to form vesicles coated with lattice proteins, which enter the cytoplasm to form early endosomes [27]. By this time, proteins, lipids, or nucleic acids in the cytoplasm are specifically sorted and packaged to form multiple intracavitary vesicles (ILVs) [28]. And exosomes are secreted when early endosomes specialize into polyvesicles (MVB) through inward budding of ILVs [25,29]. Finally, MVB fuses with the plasma membrane, releasing the exosomes into the extracellular space [30].

Exosomes are biological nanostructures that are 30–150 nm in size and compose of lipids, proteins, nucleic acids and other bioactive substances [31,32], including proteins involved in MVB biogenesis (Alix, Tsg101), heat shock proteins (Hsp70, Hsp90), and tetraspanins (CD9, CD63, CD81, CD82) and other proteins (enzymes, epidermal growth factor (EGF) receptors, metabolic molecules), *etc.* [33]. Once exosomes are released from the cell surface, they are internalized by the recipient cell, leading the recipient cells to undergo phenotypic and behavioral changes [34,35]. In general, there are three main mechanisms by which exosomes enter recipient cells: (1) direct fusion of exosomes with cell membranes, (2) interaction with cell surface receptors (ligand-receptor interaction), and (3) uptake of exosomes by recipient cells through endocytosis [36,37]. Therefore, exosomes are an important communication medium between cells: on the one hand, they can transfer endogenous bioactive molecules (such as RNA, proteins and lipids) to the recipient cells through endocytosis or direct fusion with the plasma membrane [36,38]; on the other hand, they can directly interact with the extracellular matrix or trigger reactions inside and outside the microenvironment to perform therapeutic functions [28].

Skin wound healing is a highly ordered process involving four interrelated and overlapping phases of hemostasis, inflammation, proliferation and remodeling [39]. Exosomes deliver proteins,

mRNA, microRNA, and other signaling molecules to target cells in the skin, mediating essential information transfer and cell-to-cell communication necessary for maintaining cellular function and tissue homeostasis [40]. In this section, we describe the biological functions and mechanisms of action of cell-derived exosomes in promoting different stages of skin wound healing as shown in Fig. 1A.

2.1. Hemostasis stage

Hemostasis phase occurs immediately after tissue injury. Firstly, endothelial cells are stimulated, leading to vasoconstriction and reduced bleeding [41]. Secondly, platelets are activated and undergo changes in shape, resulting in the release of platelet secretory proteins such as platelet factor, sphingosine-1-phosphate, and fibrinogen, initiating the coagulation cascade [42]. Platelets quickly adhere and aggregate on the injured endothelium, forming a platelet plug to reduce blood flow [43]. Additionally, platelet-derived exosomes play a crucial role in clot formation and promoting hemostasis. Platelet-derived exosomes have a high affinity for fibrinogen, allowing platelets to extend into the fibrinogen network and contract through platelet microfilaments and myosin, making the clot more stable and facilitating fibrin clot formation [44]. It has been confirmed that platelet-derived exosomes can generate superoxides through nicotinamide adenine dinucleotide phosphate oxidase-1 (NOX-1) mediated pathways, enhancing fibrinogen binding and activating platelets to promote hemostasis [45].

2.2. Inflammation stage

During the inflammatory phase, it has been reported that extracellular vesicles derived from M2 macrophages can reduce the levels of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), while increasing the production of vascular endothelial growth factor (VEGF), thereby preventing secondary damage at the skin wound site [46,47]. $CD4^+$ T helper 2 (T_H2) cells and regulatory T cells (Tregs cells) secrete cytokines such as IL-4, IL-10, and transforming growth factor-beta (TGF-β) to favor the transition of macrophages towards an immunomodulatory M2-like phenotype. Like parent cells, exosomes from mesenchymal stem cells (MSCs) also play a role in macrophage polarization, regulation of Treg cells, and T_H2 cells immune responses [48]. Exosomes derived from stem cells of human deciduous teeth (SHED) can regulate macrophage function through protein kinase B (AKT), extracellular regulated protein kinases (ERK1/2) and signal transducer and activator of transcription 3 (STAT3) signaling pathways to enhance autophagy and accelerate wound healing [49]. These studies indicate that exosomes from different cellular origin can regulate inflammatory responses, protect injured tissues and accelerate wound healing.

2.3. Proliferation stage

As the inflammation subsided, a proliferative period characterized by cell proliferation and migration begins [50]. Some lipid classes of exosomes (*e.g.*, sphingolipids, glycerophospholipids) have been proved to restore the formation and maturation of capillary networks and coordinate the proliferation/migration of endothelial cells at wound sites by adjusting the expression of VEGF [51], platelet-derived growth factor (PDGF) [52], and fibroblast growth factor-2 (FGF-2) [53]. For instance, exosomes derived from human amniotic endothelial cells intensify capillary density and diabetic wound closure [50]. Besides, fibroblasts play a significant role in collagen synthesis, proteoglycans production, and other granulation tissue components, contributing to the restoration of skin tissue structure [54]. It has been reported that exosomes derived from keratinocytes can enhance fibroblast migration and promote fibroblast-mediated angiogenesis by activating the phosphatidylinositide 3-kinases (PI3K)/AKT pathway or Ras homologous family member-yes-associated protein (Rho-YAP) signaling pathway, suggesting their involvement in fibroblast activation and neovascularization through cellular crosstalk [55]. Researchers discovered that exosomes from MSCs can internalize and boost the proliferation and migration of fibroblasts by up-regulating miR-21–5p under the stimulation of Fe_3O_4 nanoparticles and static magnetic fields, to perfect the angiogenic function and thus drive wound healing [56].

2.4. Remodeling stage

During the remodeling phase, the organized and sufficient deposition of collagen protein is a crucial step in wound healing [57]. Fibroblasts continuously secreted new extracellular matrix (ECM), replacing the initial granulation tissue and continuously strengthening and hardening the ECM [58]. Fibroblasts are the main stromal cell type involved in the deposition and remodeling of ECM [59]. Hu *et al.* investigated that compared to monolayer cultured cells, the exosomes secreted by human fibroblast spheroids in three-dimensional culture significantly downregulate TNF-α and upregulate TGF-β, leading to increased expression of type I collagen and a significant decrease in matrix metalloproteinase-1 (MMP-1) expression. This induction promotes effective collagen synthesis, thereby improving skin photoaging and demonstrating potential for preventing and treating skin aging [60]. Similarly, exosomes derived from autologous dermal fibroblasts and adipose mesenchymal stem cells have also been certified in several studies to accelerate collagen synthesis and promote the healing of diabetic wounds [61].

3. The origin and engineering methods of exosomes

3.1. Isolation and purification of exosomes

In order to realize the potential utility of exosomes in various biomedical fields, it is of great significance to isolate and extract exosomes and analyze their composition and function [62]. Currently available exosome separation and purification techniques are based on their size, surface charge, or immunoaffinity. There is no “one size fits all” approach as these techniques all have advantages and limitations. For example, ultracentrifugation is the gold standard for exosome extraction. This method has the advantages of simple operation, but it is costly and time-consuming, and exosome aggregation exists [63]. The size-based separation techniques mainly include ultrafiltration centrifugation and size-exclusion chromatography. Ultrafiltration centrifugation is simple, time-saving and does not affect the bioactivity of exosomes, but its purity is low. Exosomes obtained by size-exclusion chromatography have a high purity, but a long cycle. The method based on immunoaffinity is to isolate exosomes using the principle of binding antibodies to exosome surface specific antigens [64]. It can ensure the integrity of exosomes, but the cost is high and it is not easy to popularize. The precipitation method based on polyethylene glycol (PEG) is simple to operate and has high yield, but it is easy to precipitate some non-exosome pollutants [65]. Microfluidic is a technique for microscale separation based on the physical and biochemical properties of exosomes. The method is fast and easy to operate but lacks large-scale clinical sample testing [66]. While no single technique is perfect, combining the above techniques may be a solution to meet the multiple requirements for exosome isolation and purification simultaneously.

3.2. Natural exosomes

Natural exosomes are mainly derived from endogenous cells and carry functional molecules from progenitor cells that can be taken up by target cells through specific binding [67]. In consequence, the concept of utilizing exosomes as a therapeutic and diagnostic tool for diseases stems from the role of natural exosomes in intercellular communication [24].

3.2.1. Stem cells-derived exosomes

(1) Human umbilical cord mesenchymal stem cells (HucMSCs): HucMSCs have the potential of high proliferation, self-renewal and multi-function [68]. Studies have found that HucMSCs-derived exosomes (HucMSCs-Exos) exhibit similar efficacy to HucMSCs in a variety of diseases, such as inhibiting apoptosis, anti-inflammatory, and promoting tissue regeneration [69]. Single-cell sequencing showed that HucMSCs-Exos could up-regulate the expression of chemokines (CXCL3, CCL4) and CD33, thereby inducing neutrophil functionalization and timely clearing of cell debris [70]. At the same time, miR-181c in HucMSCs-Exos played a key role in regulating inflammation, reducing nuclear factor kappa-B (NF-κB)/p65 activation by targeting Toll-like receptor 4 (TLR4) to inhibit burn-induced inflammation, which may provide a potential target for clinical treatment [71]. And fibroblasts could be recruited and stimulated to secrete nerve growth factor (NGF), playing a crucial role in skin nerve regeneration [72]. The great thing was that HucMSC-Exos contains angiopoietin-2 (Ang-2), which promoted the proliferation, migration and tube formation ability of human umbilical vein endothelial cells (HUVECs), thus exerted a positive effect on vascularization [73]. Nevertheless, the mechanisms underlying these benefits are unclear and most studies have been conducted only in animal models. The utility of HucMSCs-Exos in human clinical trials should be further investigated.

(2) Adipose-derived stem cells (ADSCs): ADSCs are isolated from adipose tissue and possess the ability of multi-lineage differentiation, high proliferation and self-renewal characteristics [74]. ADSCs-derived exosomes (ADSCs-Exos) are key components of ADSCs-paracrine and exhibit various biological functions, attracting considerable interest from researchers [75]. ADSCs-Exos have been demonstrated to promote skin wound healing by regulating human dermal fibroblasts (HDFs), human immortalized epidermal cells (HaCaTs), and other major target cells through various signaling pathways [76]. Over expression of nuclear factor erythroid 2-related factor 2 (Nrf2) by ADSCs-Exos can promote endothelial cell proliferation, accelerate vascularization, and significantly reduce ulcer areas in the feet of diabetic rats to expedite wound healing [77]. In hypertrophic scars, ADSCs-Exos can reduce the levels of pro-fibrotic protein by inhibiting TGF-β2/Smad3 and Notch-1 signaling pathways, regulate the balance of collagen proportion, and further suppress the abnormal deposition of ECM, which may be a future candidate for the treatment of keloid [78]. ADSCs-Exos, which was rich in small interfering RNA (siRNA), can be directly absorbed by epithelial cells and the skin, cut down the expression of inflammatory factors such as IL-4, IL-23 and TNF-α, reinforce skin hydration and barrier function [79]. In a word, although ADSCs-Exos play a precise control role in various stages of wound healing, it is still necessary to further develop dosage standards and treatment effect evaluation strategies, to actively provide a new means to accelerate wound repair [80].

(3) Bone marrow mesenchyml stem cells (BMSCs): BMSCs are also one of the most widely used stem cells in clinical research [81]. Comparing with HucMSCs and ADSCs, BMSCs are more challenging to isolate and riskier to acquire. In various experimental models, the use of BMSCs-derived exosomes (BMSCs-Exos) has been investigated as a potential approach for future therapies [82]. Recently, studies have confirmed that BMSCs-Exos can ameliorate tissue fibrosis and promote skin wound healing by anti-apoptosis, anti-oxidation and regulating inflammation [83]. BMSCs-Exos promoted the proliferation and migration of HaCaTs through the miR-93–3p/apoptotic peptidase activator 1 (APAF1) pathway [84]. Simultaneously, BMSCs-derived exosomes inhibited the apoptosis of HUVECs by down-regulating miR-383, accelerated VEGF signaling in the skin wounds of diabetic mice, stimulated angiogenesis to realize wound healing [85]. Hu *et al*. utilized extrusion low-temperature 3D printing technology to prepare a porous hydrogel scaffold (SIS/MBG@Exos) for acellular small intestinal submucosa (SIS) combined with mesoporous bioactive glass (MBG) and BMSCs-Exos. The results of animal experiments showed that the use of SIS/MBG@Exos hydrogel scaffolds can increase the blood perfusion of wounds, shorten the length of wounds, and facilitate collagen deposition, thus offering a promising and innovative approach for the treatment of diabetic wounds [86]. Although BMSCs-Exos have been widely advertised in skin wound repair and have achieved promising results, the mechanism of influence on chronic wounds still needs to be further explored to facilitate early clinical transformation.

(4) Induced pluripotent stem cells (iPSCs): iPSCs have the potential to differentiate into any cell lineage in the body and possess regenerative properties [87]. Recently, iPSCs-derived exosomes (iPSCs-Exos) have been shown to possess therapeutic benefits for wound healing [88]. Subcutaneous injection of iPSCs-MSCs-Exos at the wound site in rats has been found to be beneficial for rapid epithelialization, reduced scar area and collagen maturation [89]. In addition, Kobayashi *et al*. reported that treatment of diabetic ulcer wounds in mice with undifferentiated iPSCs exosomes resulted in faster closing rates and better healing. To assess the potential of iPSCs-Exos in human clinical trials, Lu *et al*. treated wounds with exosomes derived from allogeneic rhesus monkey iPSCs. They observed rapid epithelialization, collagen deposition and angiogenesis in skin wounds [88]. Recent studies have found that iPSCs-Exos can also be utilized to treat skin aging. Pretreatment of HDFs with iPSCs-Exos can inhibit the cell damage caused by ultraviolet radiation b (UVB) irradiation and the overexpression of matrix metalloproteinases (MMP1/MMP3), while increasing the expression level of type I collagen in HDFs [90]. Despite these encouraging advances, the biological distribution and safety of iPSCs-Exos *in vivo* warrant careful consideration, and more investigation and research may be needed in different disease models [91].

(5) Epidermal stem cells (ESCs): Skin has a strong capacity to repair itself due to its abundance of ESCs. ESCs near the wound edge would migrate to the wound surface to speed up re-epithelialization after skin injury [92]. Studies have confirmed that ESCs and their exosomes (ESCs-Exos) can accelerate wound healing. ESCs-Exos rich in miR-203a-3p can recruit macrophages, reduce the expression of suppressors of cytokine signaling 3 (SOCS3) in macrophages, induce macrophages to polarize to M2 and release anti-inflammatory factors by activating the JAK2/STAT3 signaling pathway [93]. Additionally, the expression of the collagen fiber was more denser and uniform in the mouse diabetic foot ulcer model [79]. There was evidence that ESCs exo-

somes inhibited TGF-β3 and its downstream gene activity by up-regulating substrates miR-1, let-16a, miR-7–425p, and miR-5–142p to reduce inflammation, enhance proliferation of fibroblasts at the wound site while inhibiting their excessive activation and stimulate angiogenesis, thus promoting the regeneration of damaged skin and reducing scar formation [94].

3.2.2. Macrophage-derived exosomes

The inflammatory phase is an inevitable stage of skin wound healing and is closely related to the regulation of macrophages. Excessive activation of M1 will aggravate tissue damage, while inhibition of M2 activation will impair skin healing ability [95]. In addition, M2 macrophage-derived exosomes (M2-Exos) can regulate host defense and inflammation by inducing immune cell differentiation, activating corresponding receptor cells, and regulating the release of inflammatory mediators [96]. Zhang *et al*. found that M2-Exos targets phosphatase and tensin homolog (PTEN) *via* miR-21 to activate the AKT/mTOR signaling pathway, regulate the extracellular matrix microenvironment, and create positive conditions for angiogenesis in full-layer skin wound tissue [97]. A study based on M2-derived exosomes indicated that subcutaneous injection of M2-Exos into wound margins promotes macrophage reprogramming, thereby reducing the M1/M2 ratio to enhance angiogenesis, re-epithelialization, and collagen deposition to accelerate wound healing [98]. Therefore, we believe that macrophage-derived exosomes are also potential candidates for wound treatment. However, stable and efficient methods are needed to avoid exosomal heterogeneity during phenotypic treatment of macrophages.

3.2.3. Fibroblast-derived exosomes

In the process of wound healing, cytokines such as PDGF and epidermal growth factor (EGF) were recruited at the wound site to activate fibroblasts, stimulate their proliferation, and induce the production of collagen fibers [99]. According to reports, exosomes derived from autologous dermal fibroblasts have been reported to promote diabetic skin wound healing *via* the AKT/β-catenin pathway [100]. Interestingly, exosomes mediated miR-125b/Sirt7 signaling from young fibroblasts significantly enhanced the abundance and wound healing of myoblasts in older mice and improved dysfunctional extracellular matrix deposition, which may provide new ideas for therapeutic targets for wound healing in older adults [101].

3.2.4. Endothelial progenitor cells (EPCs)-derived exosomes

EPCs are heterogeneous populations of monocytes capable of migrating and differentiating at wound sites or performing paracrine functions. Consequently, EPCs-derived exosomes (EPCs-Exos) are attractive candidates for cell-free therapies and novel drug delivery systems [102]. Many studies have shown that EPCs-Exos has higher stability, biocompatibility and low immunogenicity, and can reduce inflammation by regulating immune cells and oxidative stress levels, showing excellent efficacy in wound healing. In addition, EPCs-Exos can inhibit the apoptosis of HaCaTs in high glucose environment [103]. By up-regulating angiogenis-related factors, miR-126, miR-182–5p and miRNA-221–3p were transmitted, and PI3K/AKT and mitogen-activated protein kinase (MAPK)/ERK1/2 signaling pathways were activated to promote vascularization and epithelialization and accelerate wound healing in chronic diabetes [102,104]. Overall, EPCs-Exos may offer promising prospects for innovative cell-free therapies to treat chronic wounds.

3.2.5. Plant-derived exosomes

Plant-derived exosomes play an important role in intercellular communication, information transfer and homeostasis. Their morphology and release mechanism are similar to mammalian origin extracellular vesicles [105]. However, plant-derived exosomes have higher yield, shorter extraction cycle and lower immunogenicity comparing with exosomes derived from mammalian [106]. Besides, some studies have found that exosomes from plants play an important role in wound repair. Ginseng-derived exosomes have been proved to possess the ability to regulate skin cell proliferation to promote wound healing and reduce inflammation [107]. Wheat-derived exosomes have a significant proliferation and migration effect on endothelial, epithelial and dermal fibroblasts, enhance the expression of wound healing related genes, and coordinate the formation of blood vessels to accelerate wound healing [108]. Huang *et al*., used multifunctional fusion nanovesicles designed with grapefruits-derived exosomes with anti-inflammatory and antioxidant effects, can target lesions to treat autoimmune skin diseases [109]. Overall, the continued development of plant-derived exosomes will facilitate their clinical application.

3.3. Engineering exosomes

Despite the therapeutic potential of natural exosomes, to enrich the function of exosomes, researchers have also invested significant efforts to modify exosomes. As a result, engineered exosomes have expanded rapidly in the past decade, primarily through two approaches: parental cell preconditioning and direct exosomal modification, as shown in Table S1 (Supporting information) [110].

3.3.1. Preconditioning of parent cells

(1) Genetic engineering: Genetic engineering is mainly a means of using transfected, viral or non-viral vectors to guide the gene sequence of proteins or peptides to fuse with the gene sequence of selected exosome membrane proteins, thereby effectively loading therapeutic substances [111]. By using transfection reagents, certain plasmids are delivered into cells to produce the desired nucleic acids, proteins, or peptides in an ectopic manner, which are then packaged into exosomes [112]. Jiang *et al*. transfected MSCs to establish TNF-stimulated gene-6 (TSG-6) overexpressing cells. In the mouse models, exosomes derived from genetically modified TSG-6 MSCs prevented scar formation, reduced local inflammation, and promoted collagen deposition during wound healing process [113]. While effective and somewhat targeted, genetic engineering approaches still have limitations, such as high cost and inability to be applied to molecules other than genetically encoded peptides and proteins [114].

(2) Pretreatment: Pretreatment of parent cells with drugs, cytokines, chemical agents or physical factors can optimize the function of parent cells, offering a more direct, safer and universal approach [45,115]. Sun *et al*. utilized isoproterenol to induce HucMSCs to be cultured in a hypoxic environment, resulting in the development of TGF-β1-enhanced exosomes (EMs). EMs rich in TGF-β1 imparted migration characteristics and enhanced stem cell properties to epidermal keratinocytes. Treatment with EMs also improved the quality of epidermal tissue repair and restored the structural and functional characteristics of sweat glands (SGs) quickly [116]. Some potential cytokines are also candidates for parental cells preconditioning. It is interesting to note that pre-treating MSCs with interferon gamma (IFN-γ) results in the secretion of exosomes with anti-inflammatory and pro-angiogenic properties [117].

3.3.2. Direct modification of exosomes

(1) Electroporation: As one of the most commonly methods for packaging cargo into exosomes, electroporation is a tem-

porary destruction of the phospholipid layer under the action of a high intensity electric field to instantaneously improve the permeability of the exosome membrane, allowing the absorption of drugs, proteins, or nucleic acids [118]. Although this method is stable and efficient, high-voltage pulse will lead to significant exosomes cracking, and only part of which can complete membrane repair, resulting in low recovery efficiency [119]. Therefore, excessive exosomes need to be invested. Hence, it is necessary to monitor this process and optimize relevant parameters such as the volume ratio exosome/loaded substance, electroporation parameters (*e.g.*, voltage), and the concentration of loaded bioactive molecules/drugs to ensure successful loading and avoid instability of the active substances [120].

(2) Ultrasonic treatment: Transient ultrasound treatment can open transient pores on the plasma membrane, temporarily increasing the permeability of the exosome membrane, allowing the diffusion of bioactive substances/drugs into the exosomal cavity [121]. With the disappearance of shear force, the exosome membrane may recover its integrity, but its size may change. At the same time, it is not suitable for delivering certain therapeutic RNA as ultrasound treatment can induce their aggregation and degradation [122]. In addition, bioactive substances/drugs may partially adsorb on the exosome membrane and partially encapsulate in the exosome, resulting in an asymmetric loading [123]. Therefore, a two-stage release of active substances may be observed in studies, with an initial burst release from the surface followed by a slow release from the core [124].

(3) Extrusion: The extrusion method involves loading a mixture of bioactive substances/drugs and exosomes into an extruder with a porous membrane ranging from 100 nm to 400 nm and loading bioactive substances/drugs into the exosomes through membrane rupture [125]. Although the loading efficiency of this strategy is relatively high, the structure and some physicochemical properties of exosome membranes have been changed due to the application of high mechanical force [124]. Kim *et al*. explored a micro-extruder with a polycarbonate membrane filter to load melatonin into extracellular vesicles. This melatonin-loaded nano-visible substance advanced transdermal delivery of melatonin and enhanced the therapeutic efficacy of atopic dermatitis by inhibiting local inflammation, mast cell infiltration, and fibrosis [123,126].

(4) Freeze-thaw cycle: The freeze-thaw cycle in a process that involves incubating exosomes with bioactive molecules/drugs at room temperature or 37 °C for a certain period, followed by freezing them under liquid nitrogen conditions, and subsequently thawing them at room temperature [127]. Hybrid exosomes formed by freeze-thaw method combining exosomes with polymer nanoparticles (such as liposomes) can not only address the issues of poor stability and rapid degradation of exosomes, but also optimize the disadvantage of poor functional polymer nanoparticles [54]. To increase targeting efficiency, Goh *et al*. proposed the use of cell-derived nanovesicles combined with liposomes to generate EXOPLEXs as a chimeric drug delivery platform. Although freeze-thaw method is simple, it has lower drug loading efficiency compared to ultrasound or extrusion methods, and it may lead to protein inactivation, exosome size change and aggregation during the freeze-thaw process [128].

(5) Surface permeator treatment: Surface permeator treatment is exploration of using surfactants such as saponins or triton to interact with cholesterol on the exosome membranes to increase the permeability of the exosome membrane [129]. This method is suitable for loading small hydrophilic molecules into the exosomes. Although surface permeator-based strategy emerges higher loading efficiency compared to simple incubation, the use of surface permeators can affect the stability and functionality of exosomes, necessitating additional purification steps to remove the surfactants [130].

(6) Chemical modification: Chemical modification allows for direct conjugation of targeting ligands or therapeutic molecules to the surface of exosomes through non-covalent conjugation or chemical bonds, as shown in Fig. S1 and Table S2 (Supporting information) [131]. Click chemistry as an effective chemical coupling reaction mechanism has attracted great attention [132]. It is a fast selective reaction with high yield and high specificity, making it suitable for exosomes surface modification [133]. Among the different kinds of click reactions, copper was often chosen to catalyze the azide alkyne cycloaddition (CuAAC) to form triazole bonds as it allowed for rapid and efficient bonding between molecules and exosomes [134]. Smyth *et al*. have taken advantage of cross-linking between the acetylene group and exosomes surface proteins to functionalize the exosomes surface. Azide-fluor545 (the azide model) was then combined with the alkyne group, and it was found that this modification did not affect the size of the exosomes and their adhesion and internalization to the target cells [135]. Nonetheless, chemical modification by click chemical reaction is not site-specific and cannot determine which amino groups or proteins on the exosomes surface will react with, so it may change or mask the active sites of other proteins on the exosomes surface [136]. Besides, secondary purification of exosomes is required to remove unreacted chemicals in a timely manner, increasing the chances of complexity and exosome loss [137].

(7) Incubation: Passive loading is the co-incubation of exosomes with bioactive molecules/drugs, taking advantage of the concentration gradient to allow the molecules/drugs to enter the exosomes membrane [138]. Although this method is simple and maintains the integrity of the membrane, it has low sample loading efficiency and cannot control the dose of bioactive molecules/drugs distributed into the exosome membrane [139].

The overview of natural exosomes and engineering exosomes is shown in Fig. 1D and Table S3 (Supporting information). In general, engineering exosomes not only retain the desired characteristics of natural exosomes, such as good biocompatibility, low immunogenicity and cell communication ability, but also have higher precision and advantages in specific biological activity and therapeutic targeting. Therefore, they significantly improve the specificity, efficacy and safety of exosome-based therapies, thus showing high clinical application value.

4. Application of biomaterial-assisted exosome biomimetic engineering strategy in skin wounds

4.1. Design strategies

Biomimetic hydrogels constructed from biomaterials have a similar structure to the natural extracellular matrix [140]. They not only absorb exudate from skin tissues but also provide a suitable microenvironment for the proliferation of endogenous cells at the wound site [141]. Therefore, encapsulating exosomes in hydrogels is an effective strategy to achieve sustained release of exosomes while maintaining their activity and function as shown in Table S4 (Supporting information) [142,143]. Hydrogels are mainly com-

posed of natural and synthetic polymers and are commonly combined with exosomes through methods such as dropwise addition, co-cultivation, and freeze-drying [144,145]. There are some strategies for delivering exosomes from hydrogels. For example, we can utilize the swelling properties of hydrogels to directly load exosomes into hydrogels, but this approach requires hydrogels with larger pores. However, when the pores are too large, the controlled release of exosomes cannot be achieved [146]. In addition, exosomes can be directly mixed with hydrogel precursor solutions by means of crosslinking agents or physical binding. This strategy is an attractive option for exosome encapsulation because they offer a high degree of tunability of hydrogels with controllable mechanical properties and degradation rates. However, a common problem is that added crosslinkers may be cytotoxic to biomolecules [147]. Furthermore, *in situ* gelation strategy with double syringe is also convenient and can achieve the targeted delivery of exosomes.

The controlled release of exosomes encapsulated in hydrogels to host tissues mainly occurs through diffusion and erosion: (1) diffusion involves mixing exosomes with the hydrogel precursor solution, followed by crosslinking polymerization, and over time, the exosomes slowly diffuse within the hydrogel; (2) erosion is the release of exosomes by hydrolysis and degradation of hydrogels in response to host microenvironment (such as pH, enzyme, temperature and light) under specific conditions [148]. This section will summarize and discuss the related research progress in this area.

4.2. Proteins

4.2.1. Collagen

Collagen, as one of the main components of the ECM in skin, plays a crucial role in wound healing [149]. Dressings based on collagen can mimic the ECM and accelerate the wound healing process [150]. Chen *et al*. loaded exosomes derived from ADSCs into serum albumin nanoparticles containing nanosilver, which were further encapsulated into injectable collagen hydrogel (Exos-Ag@BSA NFs/Col). The selective release of Ag and Exos in the oxidized wound microenvironment not only effectively inhibited bacteria, but also optimized the regenerative microenvironment. At the same time, Exos-Ag@BSA NFs/Col treatment group was conducive to vascularization, granulation formation and re-epithelialization by up-regulating the gene expression of PDGF, VEGF and HIF-1α. This resulted in higher wound closure rates and significantly accelerated wound healing and regeneration in diabetic mice models with silicone splint excision wounds [151]. Adipose mesenchymal stem cell-derived exosomes (ADSCs-Exos) loaded into scaffolds rich in collagen/platelet plasma also showed excellent anti-inflammatory and pro-angiogenic effects. Therefore, collagen combined with exosomes provides a new therapeutic strategy and theoretical basis for wound repair [152].

4.2.2. Gelatin

Gelatin, a hydrolyzed product of collagen, exhibits good biocompatibility, low immunogenicity, MMP mediated degradation, and retention of natural cell adhesion motifs [153]. In addition, gelatin modified with methylacrylylation (GelMA) can be crosslinked quickly under ultraviolet light to form a three-dimensional scaffold with appropriate viscosity, flexibility and strength [154]. This greatly improves the mechanical strength and degradation rate of gelatin, thus maintaining the stability of dressings. GelMA has been widely applied in the healing of skin wounds. It was reported that the microneedle patch (MN) prepared by GelMA and PEGDA can successfully fulfill the transdermal and controlled release of tazarotene and exosomes derived from HUVECs. In the mouse diabetic wound model, the remodeling, angiogenesis and re-epithelialization effects of collagen matrix in the treatment group were significantly superior to those in the pure material group, demonstrating the effective delivery of exosomes and drugs by MN patches (Fig. S2A in Supporting information) [155,156]. Wang *et al*. prepared epidermal stem cell-derived exosomes (VH-EVs) loaded with VH298, which can build up the function of HUVECs by activating HIF-α pathway. In a mouse diabetic ulcer model, GelMA hydrogel containing VH-EVs motivated the efficiency of wound healing by locally enhancing blood supply and angiogenesis, exhibiting a prominent therapeutic effect (Fig. S2B in Supporting information) [157]. Furthermore, exosomes derived from circ-Snhg11-modified hypoxia-preconditioned ADSCs, embedded in GelMA hydrogel through non-covalent interactions can reinforce proliferation, invasion and tube formation of endothelial stem cells, thereby playing a momentous role in restoring endothelial cell function and presented a new strategy for the treatment of diabetic ulcer (Fig. S2C in Supporting information) [158]. Collectively, gelatin dressings loaded with exosomes have shown great potential in promoting wound healing and regeneration. Further research and development in this field will undoubtedly contribute to the advancement of wound care and the improvement of patient outcomes.

4.2.3. Silk fibroin (SF)

SF is favored by researchers for its inherent biodegradability, mechanical robustness, signaling molecule stabilization, high water absorption, and low immunogenicity, and is considered a special wound repair material [159]. Multi-omics analysis showed that fibroin was conducive to enhancing the parocrine function of MSCs, regulating extracellular matrix deposition, angiogenesis and immunomodulation by differentially activating integrin/PI3K/AKT and glycolytic signaling pathways, and controlling the behavior of various resident cells (fibroblasts, endothelial cells and phagocytes) in the skin wound microenvironment which effectively improve skin regeneration [160]. Studies have found that encapsulating platelet-rich plasma (PRP), platelet-rich plasma-derived exosomes, and bone marrow mesenchymal stem cell-derived exosomes in a silk protein (SP)-based double-crosslinked bioactive hydrogel dressing (SP-Exos) can be used in a full-thickness diabetic ulcer wound model in rats. SP-Exos not only reduce NETosis and oxidative stress, but also persuade macrophages polarization towards the M2 phenotype, granulation tissue matrix formation, neovascularization, sebaceous gland and hair follicle regeneration, and intensified collagen deposition. It exhibited a faster diabetic wound healing rate compared to pure PRP and SP, making it a potential candidate for the next generation of diabetic wound dressings (Fig. S3 in Supporting information) [161]. The composite hydrogel prepared by fibroin protein combined with silk sericin (SS) not only possessed suitable mechanical properties to cope with complex wound environments, but also prolonged the release time of exosomes derived from HucMSCs and reinforce the vitality of fibroblasts and the ability of vascular tube formation *in vitro* studies [162]. SF-based microneedle devices have also been affirmed as an ideal carrier for delivering sensitive biomolecules. Fu *et al*. found that engineered exosomes loaded with miR146a released from silk fibroin patches exhibited excellent inhibitory effects on the NF-κB signaling pathway by targeting interleukin 1 receptor associated kinase 1 (IRAK1), leading to downregulation of numerous inflammatory cytokines. Furthermore, they discovered increased collagen synthesis, typical bundled collagen fibers, angiogenesis, and re-epithelialization, all of which accelerated diabetic wound healing [163]. In a word, SP-Exos show great promise in the field of wound healing. Their unique properties and ability to deliver bioactive molecules make them attractive options for developing advanced wound dressings.

4.3. Polysaccharides

4.3.1. Hyaluronic acid (HA)

HA is a major component of the extracellular matrix that maintains the structure and rigidity of the skin [164]. It interacts with CD44 membrane receptors on a variety of cell types, and is involved in inflammatory responses, angiogenesis, and tissue regeneration processes [165,166]. HA can be easily decorated by its abundant active groups, such as hydroxyl and carboxyl groups to produce hydrogels with various properties [167]. Li *et al*. prepared a thermosensitive hydrogel by modifying HA with diethylene glycol monomethyl ether methacrylate (DEGMA). This hydrogel, when loaded with MSCs-derived exosomes modified with miRNA 24–3p, reduced inflammation and fibrosis, and promoted the migration of epithelial cells [168]. Wang *et al*. found that encapsulating exosomes derived from MSCs in a double-network hydrogel (FHE@exo) composed of oxidized hyaluronic acid, peptides, and Pluronic F127 significantly enhanced the proliferation, migration, and tube formation ability of HUVECs *in vitro*. *In vivo*, the FHE@exo hydrogel showed better healing effects, with increased wound closure and less scar tissue formation compared to using exosomes or FHE hydrogel alone [169]. Researchers designed two HA derivatives of dihydrazide adipate modified HA (HA-ADH) and quaternary ammonium (QA) and aldehyde grafted HA (HA-QA-ALD), utilizing the Schiff base reaction to form a multifunctional hydrogel with certain injectable, self-healing and tissue adhesion properties. By accompanying M2 macrophages exosomes as a diabetic wound dressing, the hydrogel formed a protective barrier that covered the wound. The sustained release of M2 macrophage exosomes promoted wound angiogenesis, thereby accelerating the healing of diabetic wounds (Fig. S4 in Supporting information) [170,171]. In summary, the modification of hyaluronic acid to create different types of hydrogels has shown promising results in various applications. These hydrogels, when loaded with exosomes, have demonstrated potential in reducing inflammation, promoting cell migration, enhancing angiogenesis, and accelerating wound healing.

4.3.2. Chitosan

Chitosan is a partially deacetylated form of chitin, primarily derived from the exoskeletons of crustaceans [172]. Chitosan-based scaffolds are preeminent biomaterials for skin tissue engineering, as they possess biocompatibility, biodegradability, and antimicrobial properties [173]. They can also be chemically modified and attached to other polymers to strengthen their mechanical strength [174]. After modifying exosomes derived from synovial mesenchymal stem cells (SMSCs) with overexpression of miR-126–3p and loading them into chitosan hydrogel, it had a positive effect on wound healing by increasing granulation tissue formation and angiogenesis in rat skin wound models [175]. Moreover, Qian *et al*. discovered that exosomes derived from HucMSCs, with nano-silver adsorption, in combination with a moisturizing chitosan-silk fibroin-silver dressing (CTS-SF/Ag-Exos), could manage the infected wounds well. CTS-SF/Ag-Exos can effectively restrain the growth of bacteria and facilitate the proliferation of human fibroblasts *in vitro*. In addition, immunofluorescence staining of α-SMA and neurofilament protein-200 (NF-200) was positively expressed in a pseudomonas aeruginosa infected mouse skin wound defect model. This dressing enhanced wound healing by accelerating collagen deposition, angiogenesis, and nerve repair [176]. The self-healing hydrogel prepared by hydroxybutyl chitosan/oxidized-glucomannan as a carrier of BMSCs-derived exosomes, can be applied for the regeneration of full-layer wounds at the moving site. This dressing not only had certain antibacterial properties, but also accelerated skin tissue remodeling and prevent scar formation during the healing process of stretchable wounds [177]. Chitosan-based materials, when combined with exosomes, have shown promising results in promoting wound healing.

4.3.3. Sodium alginate (SA)

SA is a natural polysaccharide whose solution encounters calcium ions and can quickly undergo ion exchange to form a gel, avoiding the use of toxic chemical crosslinking agents such as glutaraldehyde and epichlorohydrin [178,179]. Therefore, SA gelation under mild conditions prevents the deactivation of active substances [180]. Tavoosidana *et al*. exploited ion crosslinking to construct alginate-based hydrogels for delivery of ADSCs-derived exosomes. In a rat full-layer skin wound model, hydrogels containing exosomes significantly enriched wound closure, collagen synthesis, and vascularization rates compared with hydrogels alone and sterile gauze [181]. To increase the applicability of alginate based bioactive scaffolds in clinical skin injury treatment, the influence of lyophilized spongy dressings encapsulated with exosomes on skin wound healing was further investigated. The study found that this strategy not only preserved the integrity of exosomes, but also expedited the formation of granulation tissue, contributing skin remodeling by up-regulating stroma-related proteins such as tenascin, decorin, epidermal growth factor receptor (EGFR) and angiogenic marker nucleolin (Ncl) (Fig. S5A in Supporting information) [182]. Zhou *et al*. prepared a sprayable alginate gel dressing packaged with human dental pulp stem cells (hDPSCs)-derived exosomes and oxygen-releasing. In a rat diabetic wound model, the continuous release of exosomes and oxygen for up to 7 days cut down the expression of hypoxic factors in fibroblasts, drove the polarization of macrophages towards M2 subtype, enriched angiogenesis and collagen deposition (Fig. S5B in Supporting information) [183]. Therefore, although the sodium alginate materials incorporating exosomes could be a tool for the treatment of skin wound under the safe concentration, further research is needed to optimize the use of sodium alginate in exosomes studies to ensure its safe and effective use in clinical applications.

4.4. Synthetic polymer

4.4.1. Polycaprolactone (PCL)

PCL, as one of the synthetic polymers approved by the Food and Drug Administration (FDA), is widely explored in the manufacture of wound dressings and is often selected as the main component of nanofibers due to its biodegradability, spinnability, and high toughness [184]. Su *et al*. established electrospinning to prepare PCL fibers, and by chemically modifying the material to increase its hydrophilicity, they were able to anchor BMSCs-Exos onto the surface of the polymer fiber network, resulting in a functionalized scaffold called Exos-PEF. Compared to the control group, as well as the pure material and exosomes group, Exos-PEF gave full play to the respective roles of the material and exosomes in the process, acting as a “recruitment agent” and “training agent” for immune cells. This synergically promoted beneficial macrophage and regulatory T cell responses in the skin wounds of mice, thus facilitating wound healing (Fig. S6 in Supporting information) [48]. In consequence, the research on PCL and exosomes has shown immense potential in wound healing.

4.4.2. Polyvinyl alcohol (PVA)

PVA is one of the most commonly exploratory synthetic polymers, capable of forming hydrogels through various methods such as physical and chemical crosslinking [185]. These PVA hydrogels are extensively emerged in a variety of biomedical applications [186]. The mechanical strength of PVA hydrogels possesses ionic response due to Hofmeister effect, allowing the micro-needle tips to match the strength of different tissues under the control of environmental ions [187,188]. Zhang *et al*. have developed a biomimetic

adaptive microneedle patch for the healing of diabetic ulcers. This dynamic intelligent delivery system consists of adjustable PVA hydrogel micro-needles encapsulating MSCs-Exos. MSCs-Exos was sustainably delivered by indwelling microneedles to actively regulate the proliferation and migration of fibroblasts, facilitate tube formation of vascular endothelial cells and inhibit M1 polarization of macrophages. Therefore, indwelling microneedles have been demonstrated to advance tissue regeneration and wound healing in diabetic rat models of full-layer skin wounds (Figs. S7A–C in Supporting information) [187]. Zeng *et al*. have created microneedle patch by doping polydopamine into PVA solution, followed by encapsulating M2 macrophages-derived exosomes within a photosensitive microneedle hydrogel (MEs@PMN). MEs@PMN hydrogel system has displayed excellent biocompatibility and significant photothermal effect. After sustained delivery of exosomes to the wound area, it can administer inflammation by down-regulating the expression of TNF-α, IFN-γ, IL-1 and inducible nitric oxide synthase (iNOS), boost the formation of granulation tissue and intensify angiogenesis to speed up skin wound healing (Figs. S7D–F in Supporting information) [189]. The combination of PVA and exosomes holds great promise in biomedical research. Further research is needed to fully understand the interactions between PVA and exosomes and to optimize their combination for wound repair.

4.4.3. PEG

PEG, as a well-known synthetic skeleton, is a flexible, water-clear polymer. PEG is broadly employed in tissue engineering and drug delivery applications due to its biocompatibility, non-immunogenicity, tissue simulation mechanical properties, and chemical versatility [190]. Researchers have developed a promising functional dressing by chemically modifying PEG or loading it with bioactive substances [191]. For example, Zhang *et al*. have designed a novel self-healing conductive hydrogel by coordinating and crosslinking four-arm PEG-SH with Ag. By selecting metformin as a model drug and ADSCs-Exos as the bioactive substance, the hydrogel achieved dual loading. It reduced mtROS and cellular ROS production by interfering with mitochondrial fission, protected F-actin homeostasis in a high glucose environment, maintained microvascular integrity and barrier function, suppressed inflammation, and promoted cell proliferation and angiogenesis, thereby facilitating chronic wound healing (Fig. S8A in Supporting information) [192]. It has been also demonstrated that the PEG smart hydrogel containing exosomes can further the proliferation and migration of HDFs, HaCaTs and HUVECs by enhancing phosphorylation of AKT signaling pathway. The smart hydrogel containing exosomes eliminated the adverse effects of oxidative stress on cell migration and drove diabetic wound healing by contributing to re-epithelialization, collagen deposition and neovascularization (Fig. S8B in Supporting information) [193]. Kim *et al*. designed a hydrolytically degradable PEG hydrogel delivery system that encapsulated macrophages-derived exosomes (Exogels) by controlling crosslinking density and sealing property. Exogels provided a promising therapeutic strategy for balancing pro- and anti-inflammatory immune responses during wound healing. Exogels exhibited superior performance in stabilizing closure of full-thickness skin wounds and enhanced dermal adipogenesis and hair follicle regeneration during the healing process (Fig. S8C in Supporting information) [194]. PEG has emerged as a valuable tool for loading exosomes, making them more suitable for skin wound therapy. However, further studies are required to overcome existing challenges and fully exploit the potential of PEG and exosomes in clinical applications.

4.4.4. Polyurethane (PUAO)

PUAO is a new type of antioxidant elastomer biomaterial that plays an important role in reducing oxidative stress and providing oxygen [195,196]. Kumar *et al*. developed an oxygen-releasing antioxidant wound dressing polyurethane (OxOBand) enriched with ADSCs-derived exosomes, which promotes migration and proliferation of human keratinocytes and fibroblasts. Compared to untreated control wounds in diabetic rats, OxOBand dressing resulted in faster wound closure, enhanced collagen deposition, accelerated epithelialization, increased neovascularization, and reduced oxidative stress response. The dressing strengthened the development of mature epithelial structures, with hair follicles and epidermal morphology resembling healthy skin (Fig. S9 in Supporting information) [195]. It is worth noting that the long-term stability and degradation behavior of polyurethane-Exos composites need to be thoroughly investigated. Understanding the interactions between Exos and the polyurethane matrix over time is crucial for the development of durable and biocompatible materials in wound repair.

5. Summary and prospect

Although biomaterials-assisted exosomes for skin wound repair and regeneration have achieved good results in animal models, there is still a long way to go to evaluate exosomes-based therapies to accomplish clinical translation and application, and there are still related challenges to overcome:

(1) It is well known that exosomes inherit most of the bioactive molecules and biological properties from their parent cells, but the exact content of components such as miRNA, mRNA, proteins and lipids in exosomes is not well described. In addition, the heterogeneity of exosomes from different cell sources should not be ignored, even if exosomes from the same cell type, it is impossible to tell whether there are differences between individuals. Therefore, future studies should also consider focusing on elucidate the complex composition, biological function and intrinsic targeting ability of natural exosomes.

(2) Because the mechanisms of exosomes-based intercellular communication and interaction have not been fully explored, evaluating the safety and efficacy of exosomes-based therapies is still in its infancy. Moreover, there is evidence that exosomes may induce immunosuppression and tumorigenic risk during treatment, which remains a challenging issue for clinical translation. Therefore, a great many of experiments are needed to enhance the understanding of exosomes, such as the validation of pharmacokinetic and pharmacodynamic properties, to further determine the effective dose range of exosomes in clinical use, and to furnish the possibility of safe and effective application of exosomes.

(3) Although there are various methods for separating and purifying exosomes at present, in general, the separation procedure is costly, and the exosomes production and purity are low which leading to the specific separation cannot be completely realized. A second issue is that there are no perfect schemes for large-scale standardized production and long-term preservation of high-quality exosomes for the moment. To ensure efficacy, freshly harvested exosomes are often exploited in studies. This limitation also demands that the place of production is not too far away from the site of use to avoid any loss of efficacy during transportation.

(4) In order to ameliorate the targeting and therapeutic effect of exosomes, biomaterial-based hydrogel systems have been developed successively, but there are still many obstacles that restrict their future clinical application. For example, residual components in hydrogels or the employment of crosslinkers may be toxic; it is hard to control the formation time of pH-sensitive or temperature-sensitive injectable

hydrogels, which can easily bring about needle blockage when injecting hydrogels with syringes. Thus, the preparation scheme of hydrogels should be further optimized. Moreover, due to the differences in the *in vivo* and *in vitro* environment, the release rate of exosomes encapsulated in hydrogels *in vitro* may not be able to fully simulate the *in vivo* microenvironment, so the delivery efficiency of exosomes *in vivo* should be further explored.

In conclusion, with the rapid development in the field of regenerative medicine, exosomes have been found to possess great powers in anti-inflammatory, cell proliferation and angiogenesis, and play a key role in skin wound repair. Consequently, the future clinical application and commercialization of intelligent dressings based on exosomes therapy designed according to the dynamic and complex process of skin wound healing is worthy of expectation, and further systematic evaluation is required to achieve success.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This work was financially supported by the National Natural Science Foundation of China (No. 82030056) and Postdoctoral Innovation Talents Support Program of China (No. BX20230489).

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2024.109766.

References

[1] L.P. Da Silva, R.L. Reis, V.M. Correlo, A.P. Marques, Annu. Rev. Biomed. Eng. 21 (2019) 145–169.
[2] T. Liu, Y. Lu, R. Zhan, W. Qian, G. Luo, Adv. Drug Deliv. Rev. 193 (2023) 114670.
[3] K. Las Heras, M. Igartua, E. Santos-Vizcaino, R.M. Hernandez, J. Control. Release 328 (2020) 532–550.
[4] Y. Fang, T. Nie, G. Li, et al., Chem. Eng. J. 480 (2024) 147930.
[5] Y. Kang, L. Xu, J. Dong, et al., Nat. Commun. 15 (2024) 1042.
[6] V. Falanga, R.R. Isseroff, A.M. Soulika, et al., Nat. Rev. Dis. Primers 8 (2022) 49.
[7] P. Xin, S. Han, J. Huang, et al., Chin. Chem. Lett. 34 (2023) 108125.
[8] A. Sharma, D. Sharma, F. Zhao, Adv. Healthc. Mater. (2023) 2300556.
[9] Y. Guo, J. Huang, Y. Fang, et al., Chem. Eng. J. 437 (2022) 134690.
[10] R. Chen, T. Feng, S. Cheng, et al., Nano Today 49 (2023) 101789.
[11] O.G. Davies, S. Williams, K. Goldie, J. Control. Release 353 (2023) 1096–1106.
[12] L. Fan, C. Liu, X. Chen, et al., Adv. Sci. 9 (2022) e2105586.
[13] M. Shao, D. Lopes, J. Lopes, et al., Matter. 6 (2023) 761–799.
[14] N. Parada, A. Romero-Trujillo, N. Georges, F. Alcayaga-Miranda, J. Adv. Res. 31 (2021) 61–74.
[15] H. Zhao, Z. Li, Y. Wang, et al., Front. Cell Dev. Biol. 11 (2023) 1029671.
[16] A. Hazrati, Z. Mirsanei, N. Heidari, et al., Biomed. Pharmacother. 162 (2023) 114615.
[17] D. Mijaljica, F. Spada, D.J. Klionsky, I.P. Harrison, Autophagy. 19 (2023) 2578–2584.
[18] Y. Li, D. Hao, G. Feng, F.J. Xu, Matter 6 (2023) 1060–1062.
[19] Y. Yao, Y. Jiang, J. Song, et al., Adv. Healthc. Mater. 12 (2023) e2201989.
[20] D. Lopes, J. Lopes, M. Pereira-Silva, et al., Mil. Med. Res. 10 (2023) 19.
[21] A.K. Gaharwar, I. Singh, A. Khademhosseini, Nat. Rev. Mater. 5 (2020) 686–705.
[22] J. Mondal, S. Pillarisetti, V. Junnuthula, et al., J. Control. Release 353 (2023) 1127–1149.
[23] T. Wang, Y. Fu, S. Sun, et al., Chin. Chem. Lett. 34 (2023) 107508.
[24] J. Wei, T. Qi, C. Hao, et al., Trends Analyt. Chem. 163 (2023) 117077.
[25] Q.F. Han, W.J. Li, K.S. Hu, et al., Mol. Cancer 21 (2022) 207.
[26] V.P. Chavda, A. Pandya, L. Kumar, et al., Nano Today 49 (2023) 101771.
[27] M. Mathieu, L. Martin-Jaular, G. Lavieu, C. Théry, Nat. Cell Biol. 21 (2019) 9–17.
[28] R. Kalluri, V.S. LeBleu, Science (1979) 367 (2020) eaau6977.
[29] S.V. Krylova, D. Feng, Int. J. Mol. Sci. 24 (2023) 1337.
[30] S.B. Arya, S.P. Collie, C.A. Parent, Trends. Cell Biol. 34 (2023) 90–108.
[31] A. Pallares-Rusiñol, M. Bernuz, S.L. Moura, et al., Adv. Clin. Chem. 112 (2023) 69–117.
[32] Z. Fang, X. Zhang, H. Huang, J. Wu, Chin. Chem. Lett 33 (2022) 1693–1704.
[33] I. Kimiz-Gebologlu, S.S. Oncel, J. Control. Release 347 (2022) 533–543.
[34] M. Xu, J. Ji, D. Jin, et al., Genes. Dis. 10 (2022) 1894–1907.
[35] Z. Hao, L. Ren, Z. Zhang, et al., Bioact. Mater. 23 (2023) 206–222.
[36] A.A. Farooqi, N.N. Desai, M.Z. Qureshi, et al., Biotechnol. Adv. 36 (2018) 328–334.
[37] S. Sharma, M.K. Masud, Y.V. Kaneti, et al., Small 17 (2021) 2102220.
[38] S.I. Sawada, Y.T. Sato, R. Kawasaki, et al., Biomater. Sci. 8 (2020) 619–630.
[39] P. Martin, Science (1979) 276 (1997) 75–81.
[40] J. Cabral, A.E. Ryan, M.D. Griffin, T. Ritter, Adv. Drug Deliv. Rev. 129 (2018) 394–406.
[41] R. Mo, H. Zhang, Y. Xu, et al., Adv. Drug Deliv. Rev. 195 (2023) 114753.
[42] S. Sharifi, M.J. Hajipour, L. Gould, M. Mahmoudi, Mol. Pharm. 18 (2021) 550–575.
[43] W. Bergmeier, R.O. Hynes, Cold Spring Harb. Perspect. Biol. 4 (2012) a005132.
[44] R.S. Gaspar, P.M. Ferreira, J.L. Mitchell, G. Pula, J.M. Gibbins, Free Radic. Biol. Med. 165 (2021) 395–400.
[45] A. Joorabloo, T. Liu, J. Control. Release 356 (2023) 463–480.
[46] H. Kim, S.Y. Wang, G. Kwak, et al., Adv. Sci. 6 (2019) 1900513.
[47] K. Wang, R. Dong, J. Tang, et al., Chem. Eng. J. 430 (2022) 132664.
[48] N. Su, Y. Hao, F. Wang, et al., Sci. Adv. 7 (2021) eabf7207.
[49] Y. Xie, L. Yu, Z. Cheng, et al., J. Nanobiotechnology 20 (2022) 239.
[50] P. Wei, C. Zhong, X. Yang, et al., Burns. Trauma 8 (2020) tkaa020.
[51] J. Yang, Z. Chen, D. Pan, H. Li, J. Shen, Int. J. Nanomedicine 15 (2020) 5911–5926.
[52] J. Heo, H.C. Yang, W.J. Rhee, H. Kang, Cells 9 (2020) 639.
[53] B.F. Hettich, M. Ben-Yehuda Greenwald, S. Werner, J.C. Leroux, Adv. Sci. 7 (2020) 2002596.
[54] A. Raghav, G.B. Jeong, J. Nanobiotechnology 19 (2021) 459.
[55] D.E. Clemmer, S. Ghatak, X. Zhou, et al., ACS. Nano 14 (2020) 12732–12748.
[56] D. Wu, L. Kang, J. Tian, et al., Int. J. Nanomedicine 15 (2020) 7979–7993.
[57] A. Joorabloo, T. Liu, J. Nanobiotechnology 20 (2022) 407.
[58] R.R. Driskell, B.M. Lichtenberger, E. Hoste, et al., Nature 504 (2013) 277–281.
[59] E.J. Oh, P. Gangadaran, R.L. Rajendran, et al., Stem Cells (1981) 39 (2021) 266–279.
[60] S. Hu, Z. Li, J. Cores, et al., ACS. Nano 13 (2019) 11273–11282.
[61] Z. Han, L. Dong, A. Li, et al., Mater. Today Bio 16 (2022) 100427.
[62] J.J. Lai, Z.L. Chau, S.Y. Chen, et al., Adv. Sci. 9 (2022) e2103222.
[63] F. Tan, X. Li, Z. Wang, et al., Signal Transduct. Target. Ther. 9 (2024) 17.
[64] L.M. Doyle, M.Z. Wang, Cells 8 (2019) 639.
[65] P. Li, Kaslan M, S.H. Lee, J. Yao, Z. Gao, Theranostics 7 (2017) 789–804.
[66] X.X. Yang, C. Sun, L. Wang, X.L. Guo, J. Control. Release 308 (2019) 119–129.
[67] S.G. Darband, M. Mirza-Aghazadeh-Attari, M. Kaviani, et al., J. Control. Release 289 (2018) 158–170.
[68] L. Wang, C. Yu, T. Chang, et al., Sci. Adv. 6 (2020) eaba6357.
[69] Z. Wei, S. Hang, D.K. Wiredu Ocansey, et al., J. Nanobiotechnology 21 (2023) 188.
[70] Y. Liu, M. Zhang, Y. Liao, et al., Front. Immunol. 14 (2023) 1142088.
[71] Y. Zhang, J. Yan, Q. Sun, J. Invest. Dermatol. 140 (2020) S101.
[72] Z. Zhu, X. Zhang, H. Hao, et al., Front. Cell. Neurosci. 16 (2022) 913009.
[73] J. Liu, Z. Yan, F. Yang, et al., Stem Cell Rev. Rep. 17 (2021) 305–317.
[74] T. Liu, J. Xu, X. Pan, et al., Bioact. Mater. 6 (2021) 2467–2478.
[75] P. Hong, H. Yang, Y. Wu, K. Li, Z. Tang, Stem Cell Res. Ther. 10 (2019) 242.
[76] J. Janockova, L. Slovinska, D. Harvanova, T. Spakova, J. Rosocha, J. Biomed. Sci. 28 (2021) 39.
[77] X. Li, X. Xie, W. Lian, et al., Exp. Mol. Med. 50 (2018) 1–14.
[78] J. Li, Z. Li, S. Wang, J. Bi, R. Huo, Bioengineered 13 (2022) 8515–8525.
[79] B. Cho, J. Kim, D. Ha, Y. Yi, Cytotherapy 21 (2019) e4.
[80] J. Ma, L. Yong, P. Lei, et al., J. Mater. Chem. B 10 (2022) 9565–9577.
[81] C. Chang, J. Yan, Z. Yao, et al., Adv. Healthc. Mater. 10 (2021) e2001689.
[82] S. Rani, A.E. Ryan, M.D. Griffin, T. Ritter, Mol. Ther. 23 (2015) 812–823.
[83] X. Qin, J. He, X. Wang, et al., Front. Immunol. 14 (2023) 1256687.
[84] C. Shen, C. Tao, A. Zhang, et al., Bioengineered 13 (2022) 27–37.
[85] Z.F. Han, J.H. Cao, Z.Y. Liu, et al., Diabetes Res. Clin. Pract. 183 (2022) 109126.
[86] Y. Hu, B. Wu, Y. Xiong, et al., Chem. Eng. J. 426 (2021) 130634.
[87] S. Romanazzo, K. Lin, P. Srivastava, K.A. Kilian, Adv. Drug Deliv. Rev. 161-162 (2020) 127–144.
[88] M. Lu, L. Peng, X. Ming, et al., EBioMedicine 42 (2019) 443–457.
[89] S. Kim, S.K. Lee, H. Kim, et al., Int. J. Mol. Sci. 19 (2018) 3119.
[90] M. Oh, J. Lee, Y.J. Kim, et al., Int. J. Mol. Sci. 19 (2018) 1715.
[91] Z. Gu, Z. Yin, P. Song, et al., Front. Bioeng. Biotechnol. 10 (2022) 949724.
[92] K.R. Mesa, K. Kawaguchi, K. Cockburn, et al., Cell Stem Cell 23 (2018) 677–686.
[93] H. Yang, H. Xu, Z. Wang, et al., Diabetes Res. Clin. Pract. 197 (2023) 110573.
[94] P. Wang, G. Theocharidis, I.S. Vlachos, et al., J. Invest. Dermatol. 142 (2022) 2508–2517.
[95] B. Levi, Sci. Transl. Med. 9 (2017), doi:10.1126/scitranslmed.aap8175.
[96] M. Xiong, Q. Zhang, W. Hu, et al., Pharmacol. Res. 166 (2021) 105490.
[97] L. Lyu, Y. Cai, G. Zhang, et al., Front. Mol. Biosci. 9 (2022) 1008802.
[98] C.W. Lin, C.M. Hung, W.J. Chen, et al., Pharmaceutics 14 (2022) 2065.
[99] A. Stunova, L. Vistejnova, Cytokine Growth Factor Rev. 39 (2018) 137–150.
[100] X. Han, P. Wu, L. Li, et al., Cell Cycle 20 (2021) 616–629.
[101] W. Xia, M. Li, X. Jiang, et al., J. Nanobiotechnology 20 (2022) 14.
[102] J. Zhang, C. Chen, B. Hu, et al., Int. J. Biol. Sci. 12 (2016) 1472–1487.

[103] P. Li, G. Hong, W. Zhan, et al., Int. J. Med. Sci. 20 (2023) 468–481.
[104] J. Xu, S. Bai, Y. Cao, et al., Diabetes Metab. Syndr. Obes. 13 (2020) 1259–1270.
[105] M. Cao, N. Diao, X. Cai, et al., Mater. Horiz. 10 (2023) 3879–3894.
[106] H.A. Dad, T.W. Gu, A.Q. Zhu, et al., Mol. Ther. 29 (2021) 13–31.
[107] S. Yang, S. Lu, L. Ren, et al., J. Ginseng Res. 47 (2023) 133–143.
[108] F. Şahin, P. Koçak, M.Y. Güneş, et al., Appl. Biochem. Biotechnol. 188 (2019) 381–394.
[109] R. Huang, B. Jia, D. Su, et al., J. Extracell. Vesicles 12 (2023) e12361.
[110] J. Gao, A. Li, J. Hu, et al., Front. Bioeng. Biotechnol. 10 (2023) 1100892.
[111] J. Wang, M. Wang, N. Jiang, et al., Genes. Dis. 10 (2023) 1494–1512.
[112] X. Zou, M. Yuan, T. Zhang, et al., Mol. Ther. 29 (2021) 176–190.
[113] L. Jiang, Y. Zhang, T. Liu, et al., Biochimie 177 (2020) 40–49.
[114] D. Jafari, S. Shajari, R. Jafari, et al., BioDrugs 34 (2020) 567–586.
[115] G. Yang, S. Waheed, C. Wang, et al., Int. J. Biol. Sci. 19 (2023) 1430–1454.
[116] H. Chen, Y. Liu, Y. Liu, et al., Nano Today 45 (2022) 101531.
[117] S. Wang, F. Umrath, W. Cen, et al., Cells 11 (2022) 988.
[118] B. Tong, Z. Liao, H. Liu, et al., ACS. Nano 17 (2023) 2537–2553.
[119] G. Wu, J. Zhang, Q. Zhao, et al., Angew. Chem. Int. Ed. 59 (2020) 4068–4074.
[120] A.J. Lennaárd, D.R. Mamand, R.J. Wiklander, S.E.L. Andaloussi, O.P.B. Wiklander, Pharmaceutics 14 (2022) 38.
[121] S.Le Saux, H. Aarrass, J. Lai-Kee-Him, et al., Biomaterials 231 (2020) 119675.
[122] M.J. Haney, N.L. Klyachko, E.B. Harrison, et al., Adv. Healthc. Mater. 8 (2019) e1801271.
[123] T.G.N. Cao, J.H. Kang, W. Kim, et al., Theranostics. 12 (2022) 1247–1266.
[124] M.J. Haney, N.L. Klyachko, Y. Zhao, et al., J. Control. Release 207 (2015) 18–30.
[125] L. Sun, M. Fan, D. Huang, et al., Biomaterials 271 (2021) 120761.
[126] W. Zhang, L. Wang, H. Guo, L. Chen, X. Huang, Adv. Healthc. Mater. 12 (2023) e2202751.
[127] A. Görgens, G. Corso, D.W. Hagey, et al., J. Extracell. Vesicles 11 (2022) e12238.
[128] W.J. Goh, S. Zou, C.K. Lee, et al., Biomacromolecules 19 (2018) 22–30.
[129] M. Piffoux, J. Volatron, K. Cherukula, et al., Adv. Drug Deliv. Rev. 178 (2021) 113972.
[130] C.K. Das, B.C. Jena, I. Banerjee, et al., Mol. Pharm. 16 (2019) 24–40.
[131] A. Badria, Polymers 14 (2022) 4077.
[132] J. Zeng, C. Gu, Y. Sun, X. Chen, Adv. Healthc. Mater. 12 (2023) e2203391.
[133] L. Xu, F.N. Faruqu, R. Liam-or, et al., J. Extracell. Vesicles 9 (2020) 1779458.
[134] H. Choi, Y. Choi, H.Y. Yim, et al., Tissue Eng. Regen. Med. 18 (2021) 499–511.
[135] T. Smyth, K. Petrova, N.M. Payton, et al., Bioconjug. Chem. 25 (2014) 1777–1784.
[136] Y. Liang, L. Duan, J. Lu, J. Xia, Theranostics 11 (2021) 3183–3195.
[137] J.J. Richardson, H. Ejima, Chem. Mater. 31 (2019) 2191–2201.
[138] M.D. Hade, C.N. Suire, Z. Suo, ACS Appl. Mater. Interfaces 15 (2023) 3851–3866.
[139] Y. Wang, M. Jiang, X. Zheng, et al., Biochem. Pharmacol. 215 (2023) 115691.
[140] C.M. Madl, S.C. Heilshorn, Adv. Funct. Mater. 28 (2018) 1706046.
[141] M. Hosseini, A. Shafiee, Small 17 (2021) e2101384.
[142] B. Safari, M. Aghazadeh, S. Davaran, L. Roshangar, Eur. J. Pharm. Biopharm. 171 (2022) 50–59.
[143] F. Xiong, X. Ling, X. Chen, et al., Nano Lett. 19 (2019) 3256–3266.
[144] J. Tang, X. Jia, Q. Li, et al., Proc. Natl. Acad. Sci. U. S. A. 120 (2023) e2303822120.
[145] Y. Xu, H. Chen, Y. Fang, J. Wu, Adv. Healthc. Mater. 11 (2022) 2200494.
[146] P. Khayambashi, J. Iyer, S. Pillai, et al., Int. J. Mol. Sci. 22 (2021) 684.
[147] Y. Ju, Y. Hu, P. Yang, X. Xie, B. Fang, Mater. Today Bio 18 (2023) 100522.
[148] X. Han, W. Yi, S. Chen, et al., Nano Today 49 (2023) 101804.
[149] W. Liao, D. Yang, Z. Xu, et al., Adv. Healthc. Mater. 12 (2023) e2203054.
[150] A. Arin, M.S. Rahaman, U. Farwa, B.T. Lee, Adv. Funct. Mater. 33 (2023) 2212325.
[151] Y. Chen, M.R. Younis, G. He, et al., Adv. Healthc. Mater. 12 (2023) e2300456.
[152] Y. Wang, Y. Zhang, T. Li, et al., Adv. Mater. 35 (2023) e2303642.
[153] X. Yuan, Z. Zhu, P. Xia, et al., Adv. Sci. 10 (2023) e2301665.
[154] M. Hua, S. Wu, Y. Ma, et al., Nature 590 (2021) 594–599.
[155] M. Yuan, K. Liu, T. Jiang, et al., J. Nanobiotechnology 20 (2022) 147.
[156] J. Zhu, X. Zhou, H.J. Kim, et al., Small 16 (2020) e1905910.
[157] Y. Wang, Z. Cao, Q. Wei, et al., Acta Biomater. 147 (2022) 342–355.
[158] N. Hu, Z. Cai, X. Jiang, et al., Acta Biomater. 157 (2023) 175–186.
[159] H.A. Tran, T.T. Hoang, A. Maraldo, et al., Mater. Today 65 (2023) 244–259.
[160] Y. Zhang, R. Sheng, J. Chen, et al., Adv. Mater. 35 (2023) e2210517.
[161] B.M. Bakadia, A.A. Qaed Ahmed, L. Lamboni, et al., Bioact. Mater. 28 (2023) 74–94.
[162] C. Han, F. Liu, Y. Zhang, et al., Front. Cardiovasc. Med. 8 (2021) 713021.
[163] Q. Li, W. Hu, Q. Huang, et al., Signal Transduct. Target. Ther. 8 (2023) 62.
[164] N.G. Kotla, I.L. Mohd Isa, A. Larrañaga, et al., Adv. Healthc. Mater. 12 (2023) 2203104.
[165] M.F.P. Graça, S.P. Miguel, C.S.D. Cabral, et al., Carbohydr. Polym. 241 (2020) 116364.
[166] X. Song, L. Gu, Q. Yang, et al., Chin. Chem. Lett. 34 (2023) 108079.
[167] Q. Xu, J.E. Torres, M. Hakim, et al., Mater. Sci. Eng. R: Rep. 146 (2021) 100641.
[168] X. Sun, W. Song, L. Teng, et al., Bioact. Mater. 25 (2023) 640–656.
[169] C. Wang, M. Wang, T. Xu, et al., Theranostics 9 (2019) 65–76.
[170] P. Liu, Y. Xiong, L. Chen, et al., Chem. Eng. J. 431 (2022) 132413.
[171] Y. Xiong, L. Chen, P. Liu, et al., Small 18 (2021) 2104229.
[172] M.N. Kantak, S.S. Bharate, Carbohydr. Polym. 278 (2022) 118999.
[173] S. Cheng, M. Pan, D. Hu, et al., Chin. Chem. Lett. 34 (2023) 108276.
[174] S. Peers, A. Montembault, C. Ladavière, J. Control. Release 326 (2020) 150–163.
[175] S.C. Tao, S.C. Guo, M. Li, et al., Stem Cells Transl. Med. 6 (2017) 736–747.
[176] Z. Qian, Y. Bai, J. Zhou, et al., J. Mater. Chem. B 8 (2020) 7197–7212.
[177] D. Qin, A. Zhang, N. Wang, et al., Appl. Mater. Today 26 (2022) 101342.
[178] A. Dodero, M. Alloisio, M. Castellano, S. Vicini, ACS Appl. Mater. Interfaces 12 (2020) 1162–1171.
[179] G. Liu, Y. Zhou, Z. Xu, et al., Chin. Chem. Lett. 34 (2023) 107705.
[180] X. Guo, Y. Wang, Y. Qin, P. Shen, Q. Peng, Int. J. Biol. Macromol. 162 (2020) 618–628.
[181] S. Shafei, M. Khanmohammadi, R. Heidari, et al., J. Biomed. Mater. Res. A 108 (2020) 545–556.
[182] E. Bari, D. Di Silvestre, L. Mastracci, et al., Eur. J. Pharm. Biopharm. 155 (2020) 37–48.
[183] Y. Zhang, M. Fang, W. Xie, Int. J. Biol. Macromol. 242 (2023) 125081.
[184] J. He, Y. Liang, M. Shi, B. Guo, Chem. Eng. J. 385 (2020) 123464.
[185] M. Teodorescu, M. Bercea, S. Morariu, Polym. Rev. 58 (2018) 247–287.
[186] N. Varshney, A.K. Sahi, S. Poddar, et al., ACS Appl. Mater. Interfaces 14 (2022) 14033–14048.
[187] X. Zhang, J. Gan, L. Fan, Z. Luo, Y. Zhao, Adv. Mater. 35 (2023) e2210903.
[188] S. Wu, M. Hua, Y. Alsaid, et al., Adv. Mater. 33 (2021) e2007829.
[189] J. Zeng, Z. Sun, F. Zeng, C. Gu, X. Chen, Mater. Today Bio 20 (2023) 100649.
[190] X. Yao, C. Qi, C. Sun, F. Huo, X. Jiang, Nano Today 48 (2023) 101738.
[191] R. Li, Y. Guo, A. Dong, X. Yang, Food Hydrocoll. 144 (2023) 108921.
[192] Y. Zhang, M. Li, Y. Wang, et al., Bioact. Mater. 26 (2023) 323–336.
[193] T. Jiang, S. Liu, Z. Wu, et al., Mater. Today Bio 16 (2022) 100365.
[194] G. Kwak, J. Cheng, H. Kim, et al., Small 18 (2022) e2200060.
[195] P.A. Shiekh, A. Singh, A. Kumar, et al., Chem. Eng. J. 31 (2020) 105671.
[196] P. Ahmad Shiekh, S. Anwar Mohammed, S. Gupta, et al., Chem. Eng. J. 428 (2022) 132490.