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Stem cell-derived nanovesicles delivered by responsive hydrogels for refractory wound therapy

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The dynamic microenvironment of refractory wounds comprises a complex pathological system characterized by interconnected factors, such as persistent infection, chronic inflammation, and impaired tissue repair. These pathological cues substantially hinder the healing process and negatively impact patients' quality of life. Stem cell-derived nanovesicles (SC-NVs) offer a variety of reparative functions, including antimicrobial activity, immunomodulation, angiogenesis, enhanced cellular proliferation and migration, and scarless healing, thereby demonstrating substantial potential for tissue regeneration. However, topical administration of nanovesicles is limited by poor tissue retention and rapid clearance, which constrain therapeutic efficacy and necessitate repeated dosing. Hydrogels, by virtue of their excellent biocompatibility, high water content, and tunable physicochemical properties, represent promising drug delivery vehicles. This review systematically examines the microenvironmental features of refractory wounds and the therapeutic mechanisms of SC-NVs in counteracting them to promote healing. Notably, nanovesicles can be loaded by smart hydrogel systems to respond to wound microenvironmental cues and allow for on-demand release *via* dynamic bond cleavage or structural transformation, thereby augmenting therapeutic precision. Finally, we discuss key challenges in the clinical translation of these integrated platforms and outline their future applications in precision diagnostics and therapeutics for refractory wounds.

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1. Introduction

Refractory wounds, such as diabetic ulcers, pressure ulcers and infected burns, are significant public health concerns worldwide.[1–3] The prognosis of such wounds is affected by multiple factors, including aetiology, depth, area and degree of infection.[4,5] The presence of extensive necrotic tissue, protein rich exudate and compromised local blood supply within the wound are conducive to bacterial colonisation and biofilm formation.[6,7] Persistent infection drives excessive inflammation, which not only inhibits wound healing but may also cause life threatening complications, such as sepsis and multiple organ failure, thereby leading to increased morbidity and mortality rates.[8,9] According to 2023 estimates, approximately 10.5 million people in the United States (2.5% of the total population) are affected by refractory wounds, resulting in an annual healthcare expenditure of over $30 billion.[10] Wound healing is a highly coordinated biological process that relies on the intricate synergy of multiple cell types (*e.g.*, fibroblasts, keratinocytes, and immune cells) and bioactive factors (*e.g.*, growth factors and cytokines).[11,12] Dysregulation of this process can result in delayed healing and pathological scar formation, which severely compromises patients' functional recovery and quality of life.[13] Current treatment approaches for refractory wounds include fundamental interventions (debridement and antimicrobial therapy), biological therapies (application of functional dressings) and surgery (autologous skin grafting).[14] However, these conventional strategies are limited by severe pain, risk of antimicrobial-resistant infections, prolonged healing times, hypertrophic scarring, functional contractures and secondary donor site damage, which significantly impede clinical efficacy.

In recent years, the rapid advancement of regenerative medicine has made cell therapy a viable option for refractory wound treatment. This involves transplantation of stem cells or their derivatives into the body to facilitate the repair and regeneration of damaged tissue.[15,16] For example,

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mesenchymal stem cells (MSCs) have significant potential for the repair of refractory wounds, which is attributable to their capabilities of self-renewal, tissue repair, angiogenesis and immunomodulation.[17,18] Human embryonic stem cells (hESCs) and induced pluripotent stem cells (iPSCs) can differentiate into multiple cell types, which have a broad range of potential applications in the field of tissue regeneration.[19] Despite extensive studies demonstrating the potential of stem cells in wound healing, their clinical application remains constrained by certain risks, including potential teratogenicity, immune rejection and low survival rates of transplanted cells.[20,21] To overcome these limitations, stem cell–derived nanovesicles (SC-NVs) have received significant interest. The nanovesicles composed of bilayer membranes of stem cells exhibit analogous regenerative and reparative capabilities, as well as low immunogenicity, negligible tumorigenic risk and are able to facilitate storage or transport. By carrying natural bioactive components derived from precursor cells, such as proteins, nucleic acids and exogenous substances, they play an important role in combating infections, modulating immune responses, promoting angiogenesis, accelerating epithelialisation and inhibiting fibrosis.[22–25] Nevertheless, free nanovesicles have limitations for refractory wound healing including low tissue retention rates and high metabolic clearance.[26,27] Consequently, traditional nanovesicle-based therapeutic strategies typically depend on repeated local injections or systemic administration. Given that tissue repair is a complex and protracted process, it is difficult to maintain a sustained therapeutic concentration at the wound site. Therefore, enhancing the targeting efficacy and tissue retention of nanovesicles is a key focus of current research.

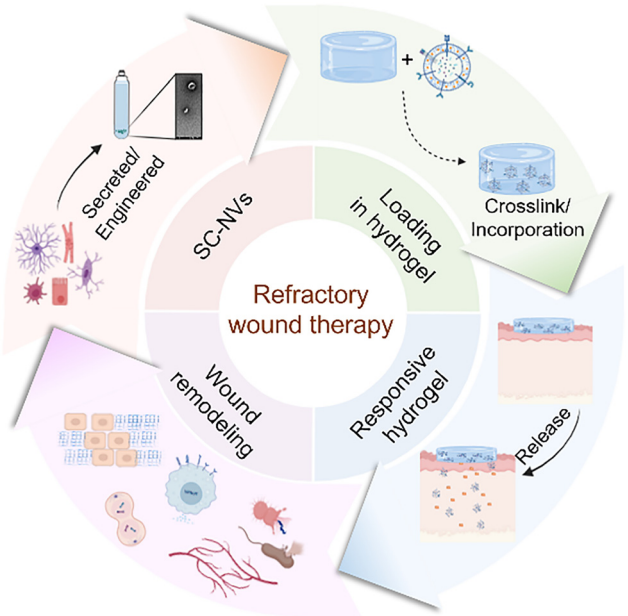

Fig. 1 An overview of the applications of SC-NVs loaded in stimulus-responsive hydrogels for refractory wound treatment (created with BioRender.com).

Hydrogel dressings, which serve as tissue repair scaffolds, have garnered considerable interest for the management of refractory wounds because of their high water content, favourable physical properties and excellent biodegradability.[28,29] These features allow them to provide structural support and enable drug delivery to the wound microenvironment.[30] This review outlines current approaches using SC-NV-based responsive hydrogels to accelerate the healing of refractory wounds. We initially discuss the microenvironmental characteristics of refractory wounds, followed by a summary of recent advances in the application of SC-NVs for the treatment of refractory wounds. Finally, we discuss the latest applications of SC-NV-based responsive smart hydrogels for the treatment of refractory wounds. Fig. 1 provides a visual representation of these approaches.

2. Pathological microenvironment of refractory wounds

Wound healing is a dynamic pathological process that typically progresses through three overlapping phases: inflammatory, proliferative, and remodelling phases.[31,32] During the inflammatory phase, coagulative necrosis and cell death occur within the wound area. The immune response is activated in this phase, which results in the release of pro-inflammatory cytokines, such as interleukins (*e.g.* IL-1β and IL-6) and tumour necrosis factor (TNF-α), which eliminate pathogens and necrotic tissue from the wound site.[33] During the next proliferative phase, fibroblasts grow extensively and synthesize collagen under the influence of factors such as transforming growth factor-β (TGF-β). Concurrently, ECs form new blood vessels under the guidance of signals such as vascular endothelial growth factor (VEGF), thereby constructing granulation tissue that supports epithelial regeneration.[34] During the remodelling phase, functional recovery of the tissue is achieved through dynamic equilibrium of collagen remodelling and degradation within the wound matrix. However, failure to effectively control infection during wound healing allows pathogens to hyperactivate the inflammatory response, thereby increasing vascular permeability. This prevents the newly formed vascular network from delivering oxygen and nutrients, thereby perpetuating tissue hypoxia. Hypoxia and persistent inflammatory signals drive the dysregulated fibroblast-to-myofibroblast transition, resulting in disordered collagen deposition and arrangement and ultimately leading to the formation of pathological scar tissue.[35,36] Therefore, a thorough understanding of the mechanisms influencing the healing process of difficult-to-heal wounds is crucial for developing targeted therapeutic strategies (Fig. 2).

2.1. Infection

The skin serves as the primary barrier of the body against pathogenic microbial invasion. Following skin injury, this function is compromised, which results in the accumulation of necrotic tissue, retention of protein-rich exudate and

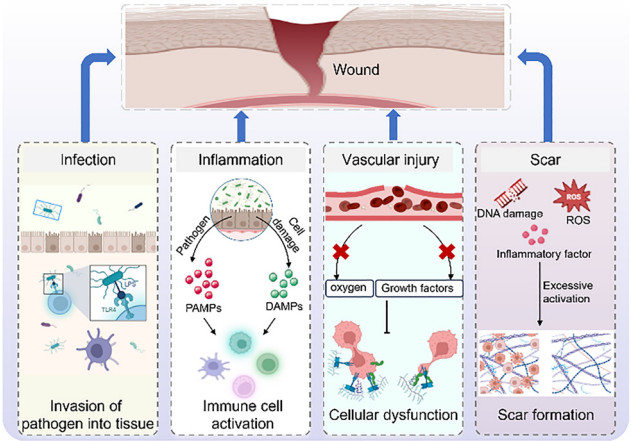

Fig. 2 Illustration of the pathological microenvironments in refractory wounds (created with BioRender.com).

increased capillary permeability.[37,38] These factors collectively create a microenvironment conducive to pathogen colonisation and proliferation.[39] The risk of bacterial infection increases with the extent of the skin damage and the depth of tissue injury. The most common wound infecting pathogens include *Staphylococcus aureus* (*S. aureus*), *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Candida* species and *Aspergillus* species.[40,41] They colonise at the wound site, disrupting the normal healing process and further suppressing the immune response. These factors converge to establish a vicious cycle of infection, prolonged inflammation and disrupted tissue repair. Moreover, prolonged pathogen colonisation facilitates biofilm formation, which prevents the migration of keratinocytes and fibroblasts, thereby severely delaying wound closure and epithelialization.[42,43] Studies indicate that the rate of biofilm associated bacterial infections in refractory wounds is 90%.[44] Currently, the clinical management of wound infections is heavily reliant on topical or systemic antibiotics and antifungal agents.[45,46] However, the structural complexity of biofilms and the barrier function of the microenvironment prevent conventional drugs from effectively penetrating and eradicating pathogens, thereby significantly delaying wound healing.[47,48] Thus, nanovesicles and hydrogels have considerable potential as their targeted drug-delivery capability offers a novel approach for treating refractory wound infections.

2.2. Inflammation

In refractory wounds, damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs) accumulate locally, activating innate immune responses through pattern recognition receptors, such as Toll-like receptors.[49] This triggers the adaptive immune response, which induces the release of numerous inflammatory cytokines and chemokines and recruits immune cells to the wound site, thereby causing an inflammatory reaction.[50] Moderate inflammation aids in the clearance of necrotic tissue and pathogens, and provides a foundation for subsequent angiogenesis and granulation tissue formation. However, the sustained activation of the TLR4/MyD88/nuclear factor kappaB (NF-κB) signalling axis driven by DAMPs/PAMPs can result in the excessive accumulation of inflammatory mediators in the wound microenvironment.[51] This uncontrolled inflammatory response not only hinders epithelialisation and exacerbates tissue damage but also triggers a systemic inflammatory response.[52,53] This systemic response is characterised by capillary leakage and the release of marked amounts of reactive oxygen species (ROS), which significantly increases the risk of secondary infection, multiple organ dysfunction and scar formation.[54,55] Therefore, remodelling the inflammatory microenvironment of the wound is important for overcoming the therapeutic challenges associated with refractory wounds.

2.3. Vascular trauma

Impaired angiogenesis, tissue hypoxia, nerve injury and abnormal extracellular matrix formation are key factors that hinder wound healing.[56] Following wound injury, the compromised vascular system immediately prevents the delivery of oxygen to the wound bed and reduces proangiogenic factors, thereby intensifying hypoxia and oxidative stress.[57–59] During short-term hypoxia, the expression of hypoxia-inducible factor-alpha (HIF-α) increases, thereby upregulating vascular endothelial growth factor (VEGF) expression.[60,61] VEGF activates endothelial nitric oxide synthase (eNOS) to promote nitric oxide (NO) synthesis, thereby enhancing endothelial cell migration and proliferation. At the same time, the hypoxic microenvironment stimulates keratinocytes directly, increasing their VEGF expression and driving endothelial cell capillary lumen formation. As capillaries form, eNOS-expressing endothelial cells produce increased levels of NO, which alleviates tissue hypoxia and ischaemia by inducing vasodilation and promoting wound healing.[62] However, the angiogenesis of refractory wounds is often dysregulated. In diabetes, elevated blood glucose and fatty acid levels suppress HIF-1α stability and function, leading to insufficient activation of HIF signaling and impaired adaptive responses to hypoxia.[63] Under the combined effects of hyperglycemia and oxidative stress, HIF-1/VEGF expression is downregulated in diabetic wounds, resulting in inadequate angiogenesis and local ischemia.[64,65] However, in venous ulcers, excessive pro-inflammatory cytokines induce excessive and disorganised angiogenesis, forming leaky, tortuous and non-functional vessels.[66] This abnormal vascularisation ultimately leads to excessive scar formation and functional impairment through collagen matrix degradation and perpetuation of chronic inflammation.[67] By modulating relevant signalling pathways at the appropriate time and intensity to restore angiogenic homeostasis, the wound microenvironment can be optimised to promote healing and reduce adverse outcomes such as fibrosis.

2.4. Scars

Wound healing is a highly dynamic process that involves a series of complex cellular and biochemical events, including acute inflammatory responses, cellular proliferation, and ultimately the formation of fibrous scar tissue characterized by

neovascularisation and immature collagen deposition. During refractory wound healing processes, interference from multiple factors often prevents dermal tissue from fully regenerating into normal skin structure.[68] In particular, in refractory wounds involving extensive or deep tissue damage, foreign body infection or recurrent ulceration, it disrupts the healing process and can result in an imbalance between anabolic and catabolic processes to promote pathological scar formation.[69] Pathological scars, such as hypertrophic scars and keloids, often exhibit increased numbers of newly formed capillaries. These vessels are structurally immature and hyperpermeable, resulting in the persistent leakage of plasma components into the extracellular matrix (ECM). The extravasated fibrinogen acts as an early signalling molecule that directly activates the TGF-β/Sma and MAD-related protein (SMAD) signalling pathway, thereby promoting fibroblast activation and abnormal collagen deposition.[70,71] Additionally, ECs can undergo endothelial-mesenchymal transition (EndoMT) to transform into myofibroblasts, which directly exacerbate the fibrotic process and promote scar formation.[72] Ultimately, they result in a lack of skin appendages, decreased mechanical properties, permanent loss of skin function, and significantly increased treatment difficulty.[73,74] Current scar intervention methods, such as silicone gel, laser therapy, and compression therapy, are often limited by inconsistent efficacy, high costs, and prolonged treatment cycles.[75] Therefore, the development of more efficient scar prevention and management strategies suitable for early intervention has significant clinical importance.

3. Role of SC-NVs in refractory wound healing

Cell-nanovesicles are composed of phospholipid bilayers that can be obtained by either the secretion of various cell types or engineered techniques. They generally appear spherical or ellipsoidal, with diameters ranging from 30 to 1000 nm and show low immunogenicity and good targeting ability.[24] Naturally secreted vesicles (such as exosomes, microvesicles, and apoptotic bodies) are predominantly harvested from cell culture supernatants. Their isolation primarily relies on separation and enrichment techniques, including differential ultracentrifugation, polymer precipitation, gel filtration chromatography, immunocapture and microfluidic technology.[76–78] In contrast, synthetic nanovesicles that have been engineered to mimic stem cell functions are generated by reconstituting isolated cellular membranes into vesicular architectures. Engineered vesicles can be produced in batches *via* mechanical extrusion, freeze–thaw cycles or ultrasonic disruption, resulting in higher yields and enabling active drug loading or targeting ligand anchoring.[79–81] Based on their origin, nanovesicles can be categorized into several types: cell-derived nanovesicles originating from various cell types (stem cells, immune cells), fluid-derived nanovesicles sourced from bodily fluids (blood, milk) and plant-derived nanovesicles obtained from herbal extracts.[22] Among these, nanovesicles derived from stem cells,

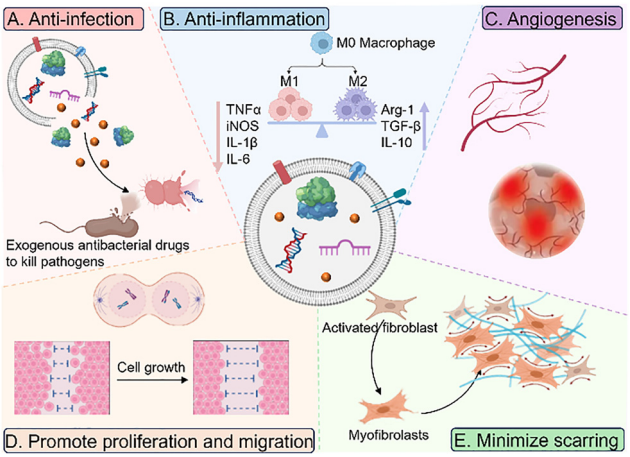

Fig. 3 Applications of SC-NVs in promoting refractory wound repairment (created with BioRender.com).

such as ESCs, somatic stem cells (SSCs), iPSCs and MSCs, have garnered significant attention due to the excellent pro-healing capabilities inherited from their cell source.[21] They can carry not only naturally bioactive molecules, such as proteins, lipids and nucleic acids (DNA, mRNA and miRNA), but also exogenous materials, such as antibiotics and phototherapeutic agents, through engineered loading.[23] Once their contents are delivered to recipient cells, nanovesicles can regulate various biological processes, including cell proliferation, differentiation, migration and immunomodulation. In this section, we describe the mechanisms of action and signalling networks of SC-NVs in refractory wounds (Fig. 3).

3.1. Anti-infection activity of SC-NVs

Because of the loss of local barrier function and the disruption of the immune microenvironment, refractory wounds are highly susceptible to bacterial infection.[82] This can result in recurrent local inflammation and persistent non-healing, which has severe consequences, including osteomyelitis, amputation or sepsis. Antimicrobial agents such as photosensitizers, antimicrobial peptides and antibiotics have demonstrated significant efficacy against pathogenic infections, including *Staphylococcus aureus*, *Candida albicans*, and *coronaviruses*. However, they often fail to reach and maintain effective therapeutic concentrations at wound sites, which can lead to the development of drug-resistant strains and exacerbating the wound.[83] Thus, there is an urgent need to develop antimicrobial drug delivery systems to control wound infections. Nanovesicles serve as advantageous carriers for drug delivery due to their inherent phospholipid bilayer structure comprising a hydrophobic membrane and hydrophilic core, causing minimal immunogenicity.[84,85] Current strategies for drug delivery using stem cell-derived vesicles primarily include two approaches: surface modification and internal loading.[86,87] In surface chemical modification, ligands such as aptamers, antibodies, or peptides are anchored to the vesicle surface *via* conjugation reactions or lipid assembly, enabling precise

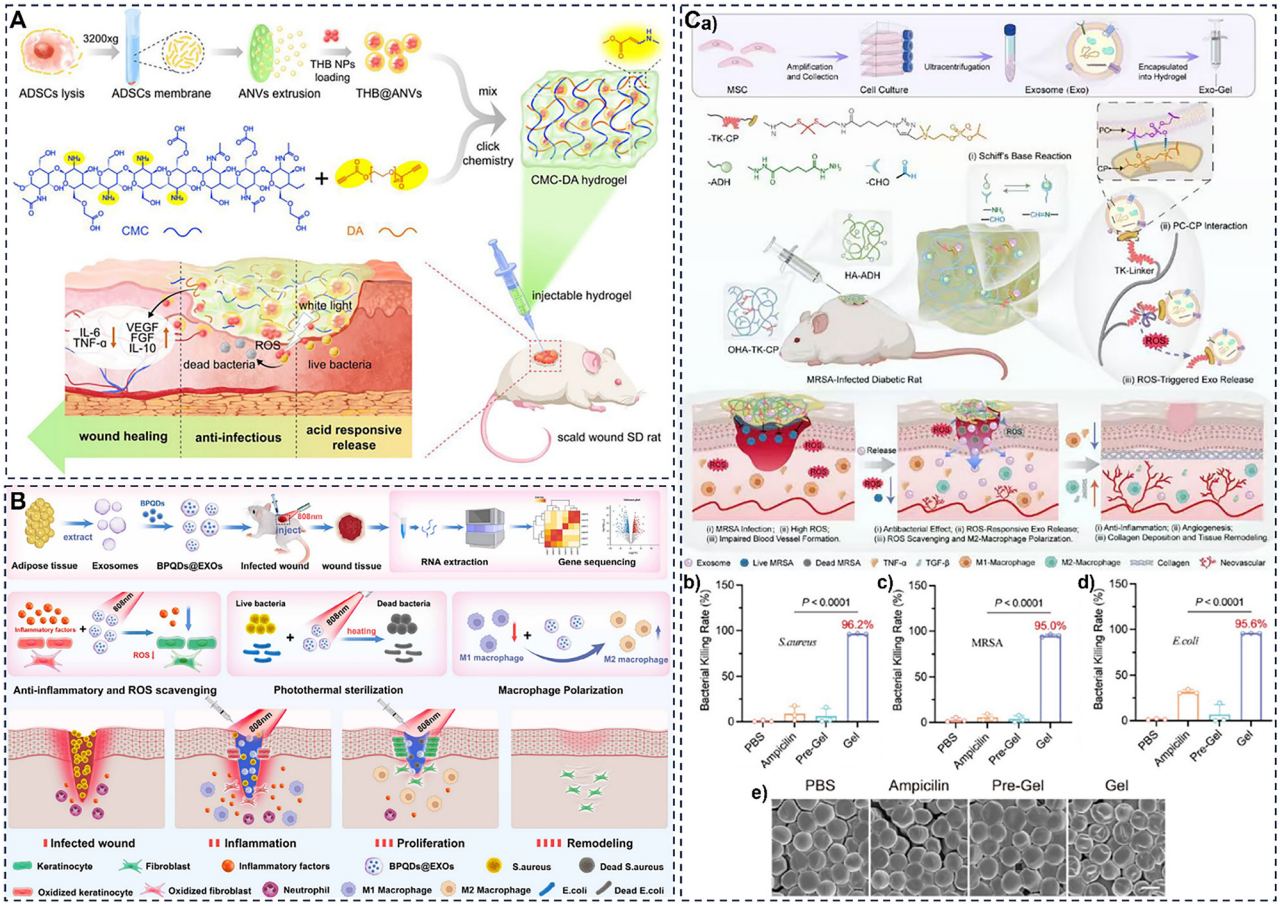

Fig. 4 (A) Schematic illustration of the mechanism of action of THB@ANV hydrogel dressings. Reproduced with permission from ref. 90. Copyright 2023 Wiley. (B) Schematic illustration of photothermal antibacterial properties of the BPQDs@EXO (BE) nanoplatform. Reproduced with permission from ref. 91. Copyright 2025 Wiley. (C) Mechanisms of the Exo-Gel system for accelerating wound healing through antibacterial activity, ROS scavenging, and exosome-facilitated anti-inflammatory and tissue regeneration effects. Reproduced with permission from ref. 92. Copyright 2025 American Chemical Society.

tissue- or cell-specific targeting.[88] Internal loading exploits the vesicle lumen and membrane stability to encapsulate therapeutic agents *via* direct incubation, sonication, mechanical extrusion or electroporation.[89] These techniques enable the development of intelligent delivery systems that combine targeting capabilities with high drug loading capacities, providing flexible engineering solutions for refractory wounds. To address the challenge of bacterial load in infected burn wounds, Chen *et al.* developed THB-functionalised nanovesicles (THB@ANVs) by combining aggregation-induced emission photosensitisers with nanovesicles derived from adipose-derived stem cells (ADSCs). This system suppressed bacterial proliferation and promoted anti-infection processes in deep burn models (Fig. 4A).[90] Wang *et al.* engineered a composite nanoplatform by integrating ADSC-Exos with black phosphorus quantum dots (BPQDs@Exos). This platform demonstrated multifunctional efficacy in infected wounds, including eradicating bacteria, reducing reactive oxygen species levels, promoting M2 macrophage polarization, and accelerating re-epithelialization (Fig. 4B).[91] Moreover, Wang *et al.* designed an adaptive multifunctional hydrogel (ExoGel), which anchors Exo *via* phosphatidylcholine groups and disrupts bacterial membrane structures. This hydrogel showed significant antibacterial and wound healing capabilities in full thickness wounds of diabetic rats infected with methicillin-resistant *S. aureus* (Fig. 4C).[92]

3.2. Inflammatory regulation function of SC-NVs

Inflammation during wound healing typically occurs within the first three days following injury. Moderate inflammation accelerates the healing process by eliminating microorganisms and degrading the injured tissue.[93,94] However, dysregulated inflammation is a hallmark of refractory wounds, which significantly delays the healing process, promotes scarring and may culminate in functional disability.[95] During the initial phase of wound healing, M1 macrophages recruit and activate immune cells by secreting pro-inflammatory cytokines (*e.g.* IL-1β, IL-6 and TNF-α) and chemokines, which facilitate the clearance of pathogens and necrotic debris. The macrophage phenotype subsequently transitions from a pro-inflammatory M1 to a reparative M2 subtype. M2 macrophages promote wound healing by secreting anti-inflammatory factors, such as IL-10 and

TGF-β, while concomitantly participating in angiogenesis and tissue remodeling.[96,97] Therefore, maintaining dynamic equilibrium between M1 and M2 macrophages is important for optimal wound healing. Impairment of the M1 to M2 transition results in a refractory inflammatory state, which is characterised by delayed wound closure, impaired angiogenesis and decreased collagen deposition.[98] Thus, modulating macrophage polarisation represents an emerging therapeutic strategy for refractory wound repair. Mesenchymal stem cell-derived extracellular vesicles (MSC-EVs) can modulate macrophage polarisation by delivering microRNAs and essential proteins that activate the PI3K-Akt signalling pathway.[99] This promotes M2 macrophage polarisation, suppresses proinflammatory cytokine secretion and facilitates tissue repair. Saccu *et al.* reported that bone marrow mesenchymal stem cell (BMSC)-derived nanovesicles attenuate inflammation in alkaline corneal burns by downregulating pro-inflammatory cytokines and upregulating anti-inflammatory factors, thereby accelerating wound healing (Fig. 5A).[100] Huang *et al.* elucidated an underlying mechanism in a mouse burn model. They found that miR-153-3p enriched in nanovesicles derived from BMSCs attenuates inflammation by inducing M2 macrophage polarisation, upregulating Arginase-1 expression and downregulating TNF-α expression (Fig. 5B).[101] In addition, nanovesicles derived from MSCs of alternative tissue origins show comparable anti-inflammatory potential. For example, human umbilical cord mesenchymal stem cell (hUCMSC)-derived Exos reduce leukocyte infiltration through high miR-181c expression. They also downregulate TLR4, NF-κB/P65 and p-P65 expression, thereby inhibiting the release of inflammatory mediators, such as IL-1β and TNF-α. This mechanism ameliorates the inflammatory response by modulating cell recruitment and cytokine production (Fig. 5C).[102] However, the production of MSC-derived extracellular vesicles (EVs) is currently limited by donor age, sex and genetic variability, as well as their limited capacity for *in vitro* expansion and loss of efficacy with extended passaging.[103,104] Together, these factors limit their potential as a scalable, reproducible therapeutic modality. iPSCs can be used to generate induced mesenchymal stem cells (iMSCs), overcoming the scalability and donor variability issues in therapeutic EV production. Daniel Levy *et al.* initially demonstrated that iPSC-derived EVs exhibit anti-inflammatory properties that are comparable with, or even superior to, those of iMSC-EVs and promote repair in diabetic mouse models.[105] Raghavendra Upadhya subsequently identified that microRNA-21 (miRNA-21), which is abundant in human induced pluripotent stem cell-derived neural stem cell-derived extracellular vesicles (hiPSC-NSC-EVs), mediates anti-inflammatory activity by downregulating NF-κB and TNF-α, while upregulating the anti-inflammatory cytokine interleukin-10 (IL-10).[106] Furthermore, embryonic stem cell-derived vesicles (ESC-EVs) demonstrate distinct immunomodulatory potential. For example, they have an abundant cargo of TGF-β, SMAD2 and SMAD4, which activates the TGF-β/SMAD signalling pathway in CD4+ T lymphocytes. This promotes regulatory T cell (Treg) proliferation and attenuates inflammatory responses.[107] However, acquiring ESC-EVs is fraught with ethical concerns, and producing them necessitates stringent culture conditions. Long-term culture frequently results in genetic instability, thereby impeding stable, uniform and large-scale production. Consequently, the iPSC technology platform, which is ethically uncontroversial and offers standardised sourcing and unlimited expansion potential, exhibits superior translational potential for producing uniform, efficient and scalable therapeutic EVs relative to ESC-EVs.

In refractory wounds, persistent inflammation drives excess ROS production, thereby inducing oxidative stress.[108] These free radicals oxidise the unsaturated fatty acids present in cell membranes and organelles, thereby initiating lipid peroxidation.[109] Lipid peroxidation degrades unsaturated fatty acids, compromising the structural integrity, fluidity, permeability, ion transport and barrier function of the membrane. This exacerbates local inflammation and disrupts the functions of reparative cells.[110] Studies indicated that SC-NVs also mitigate inflammation and tissue damage by attenuating oxidative stress. Wang *et al.* found that MSC Exos enhance endogenous anti-oxidant capacity by activating the nuclear factor erythroid 2-related factor 2 (NRF2) pathway, modulating iron homeostasis and enhancing the activity of anti-oxidant enzymes (*e.g.* glutathione peroxidase, catalase and superoxide dismutase), thus exerting anti-inflammatory effects and promoting tissue repair (Fig. 5D).[111] Moreover, microRNAs (miRNAs) encapsulated within nanovesicles can reduce oxidative stress by attenuating gene expression networks. Xiao *et al.* showed that miR-146a targeting Src, delivered by MSC-derived nanovesicles, suppressed Src phosphorylation and its downstream targets, VE-cadherin and caveolin-1. This reduced the senescence-associated secretory phenotype (SASP) in oxidative stress-induced senescent endothelial cells while restoring angiogenesis, migration and other cell functions (Fig. 5E).[112] Liu *et al.* utilized high-throughput sequencing to identify the significant upregulation of miR-192-5p in keratinocyte oxidative stress models and burn wound tissues. Engineered exosomes loaded with antagomiR-192-5p were encapsulated in MXene-modified gelatin methacrylate hydrogel, enabling sustained release, which modulated the inflammatory microenvironment and accelerated re-epithelialization in burn wounds (Fig. 5F).[113]

3.3. Angiogenesis function of SC-NVs

The skin is highly vascularised and consists of pathways for delivering oxygen, nutrients and bioactive factors to wounds while facilitating the removal of metabolic waste.[114] However, refractory wounds often exhibit significant microvascular dysfunction, characterised by reduced endothelial function, increased capillary permeability and inadequate local perfusion, which results in severe oxygen and nutrient deprivation within the wound microenvironment, thus impeding healing.[115,116] Consequently, promoting neovascularization has emerged as a therapeutic strategy for optimal wound repair. This process encompasses two primary mechanisms: angiogenesis and vasculogenesis. Angiogenesis involves new blood vessels sprouting from the existing vasculature. Adequate

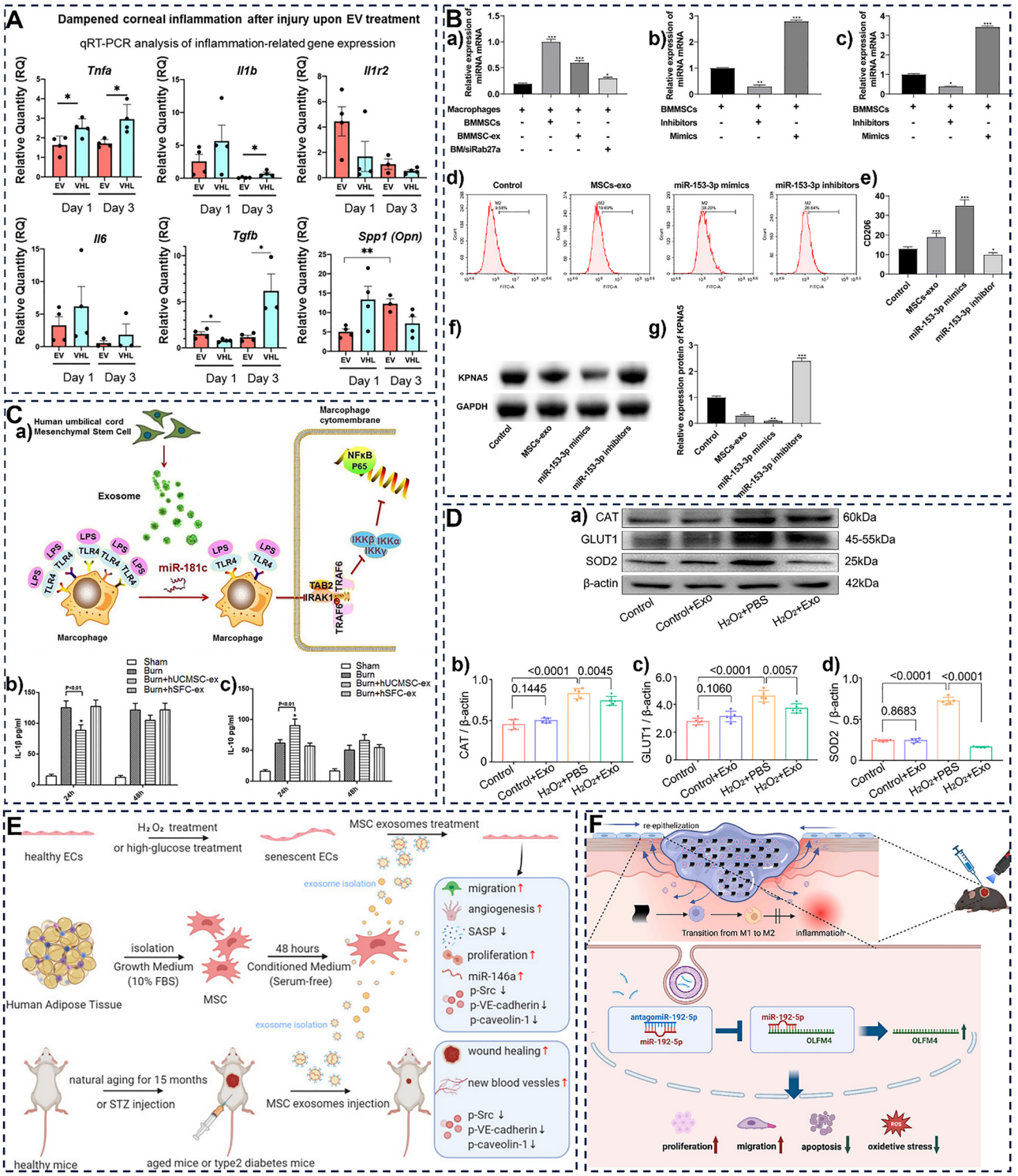

Fig. 5 (A) Dampened corneal inflammation after injury upon BMSC-EV treatment. Reproduced with permission from ref. 100. Copyright 2022 Cells. (B) BMSCs promote M2 polarization by transferring Ex-derived miR-153-3p. Reproduced with permission from ref. 101. Copyright 2025 Springer Nature. (C) Exosomes mediate MiR-181c attenuating burn-induced excessive inflammation. Reproduced with permission from ref. 102. Copyright 2016 Elsevier. (D) MSC-Exo alleviate oxidative responsiveness in H_2O_2-stimulated keratinocytes. Reproduced with permission from ref. 111. Copyright 2020 Elsevier. (E) Schematic illustrations of MSC-sEV repairments on oxidative stress – *via* regulation of the miR-146a/Src pathway. Reproduced with permission from ref. 112. Copyright 2021 Springer Nature. (F) Schematic diagram of the efficacy of the Exo-ant-192@M-Gel hydrogel in healing burn wounds. Reproduced with permission from ref. 113. Copyright 2025 Elsevier.

neovascularisation supplies granulation tissue with oxygen and nutrients and facilitates the migration and activation of reparative cells. Vasculogenesis involves the assembly of endothelial progenitor cells *de novo* to form vascular structures.[117] Endothelial cells act as the main mediators of vasculogenesis, progressively constructing functional microvascular networks through proliferation, migration and tubulogenesis. Adequate vascularization not only supplies essential oxygen and nutrients to granulation tissue but also facilitates migration and functional activation of reparative cells to accelerate healing of refractory wounds.[118,119] Proteomic analysis revealed that mesenchymal stromal cell (MSC)-derived exosomes contain critical factors, including vascular endothelial growth factor (VEGF), transforming growth factor-beta 1 (TGF-β1), interleukin-8 (IL-8) and BHLH transcription factor 1 (HES1), which are essential for their pro-angiogenic activity.[120] hUC-MSC-derived Exos deliver Wnt4, which activates the β-catenin signalling pathway. This promotes the nuclear translocation of β-catenin and regulates the expression of proliferation-associated proteins and cadherins, thereby enhancing endothelial cell proliferation, migration and tubulogenesis in a dose-dependent manner (Fig. 6A).[121] Exos derived from hUCMSCs treated with blue light showed increased expression of the miRNAs 135b-5p and 499a-3p, which synergistically inhibit MEF2C gene expression, thereby promoting human umbilical vein endothelial cell (HUVEC) proliferation and migration and significantly increasing neovascular density in a deep partial thickness burn model (Fig. 6B).[122] Optimising stem cell culture strategies can enhance the pro-angiogenic capacity of nanovesicles. Compared with conventional two-dimensional (2D) culture, three-dimensional (3D) culture augments the paracrine function of MSCs by forming spheroid aggregates that recapitulate the *in vivo* environment.[103,123] Zhu *et al.* demonstrated that 3D-culture–derived Exos promoted HUVEC tube formation to a greater extent compared with 2D- and 2.5D-culture–derived Exos (Fig. 6C).[124] The diabetic hyperglycemic environment shows reduced formation of H-type vessels (CD31 + EMCN +), which supply nutrients and oxygen and activate osteoprogenitor cells through paracrine signaling.[125,126] Liu *et al.* identified a regenerative vascular subtype coexpressing CD31 and EMCN in the deep reticular dermis that contributes to wound healing through neovascularisation and supports adjacent proliferating cells. Subsequently, they generated MSC aggregates and used Exos enriched in angiogenic proteins to deliver γ-secretase-associated proteins. This activates the Notch signalling pathway in endothelial cells and promotes angiogenesis in wounds (Fig. 6D).[127] In addition to mesenchymal stem cell (MSC)-derived exosomes, both embryonic stem cell (ESC)- and induced pluripotent stem cell (iPSC)-derived exosomes have demonstrated potential for angiogenesis. ESC-derived exosomes can improve endothelial cell senescence and restore angiogenic function by activating the Nrf2 pathway.[128] Furthermore, iPSC-derived exosomes (iPSC-Exo) significantly increase neovascularisation in diabetic wounds, thereby accelerating the healing process. While the pro-angiogenic effects of iPSC-Exo are well documented, the underlying molecular mechanisms are yet to be fully elucidated, representing a critical area for future investigation.

In refractory wounds, neurovascular network damage represents a major pathological mechanism underlying persistent healing failure. This causes local sensory dysfunction and is frequently accompanied by intractable neuropathic pain, which significantly affects patients' daily functioning and slows their recovery.[129,130] Consequently, orchestrating coordinated neurovascular regeneration is a major challenge in regenerative medicine. Chai *et al.* developed a composite hydrogel system based on mineralised metal-phenol (MMF) particles and stem cell Exos to promote full-thickness functional skin regeneration in burn wounds. In a murine deep second-degree burn model, the nanocomposite hydrogel significantly accelerated wound closure (achieving 96.9% within 15 days, 4-fold faster than controls), promoted angiogenesis and innervation (increasing vascular density by over 2-fold and nerve fibre regeneration by 3.5-fold) and facilitated scarless wound healing (with epidermal thickness comparable to native skin) (Fig. 6E).[131] Beyond material engineering approaches, functionalised nanovesicles have shown efficacy in enhancing neurovascular regeneration. Zuo *et al.* demonstrated that hypoxia-pretreated MSC Exos attenuate hypoxia-induced vascular endothelial cell injury through the microRNA-125a-5p/receptor tyrosine kinase-like enhancer of split family member 1 (RTEF-1) pathway. This enhanced neural recovery and ameliorated neuronal and vascular damage in high-altitude cerebral oedema mice, thus offering a novel regenerative medicinal strategy (Fig. 6F).[132]

3.4. Pro-proliferation and migration properties of SC-NVs

Repair of refractory wounds necessitates coordinated proliferation, migration, and functional synchronisation of multiple cell types, including fibroblasts, vascular endothelial cells (ECs), and epidermal cells.[133,134] Within this intricate process, ECs contribute to the restoration of the local microcirculation and the enhancement of oxygen and nutrient delivery. Fibroblasts are the main functional cells that mediate granulation tissue formation, tissue organisation and wound contraction.[135] Through centripetal migration from wound margins, epidermal cells complete re-epithelialisation and wound closure.[136] Therefore, precise modulation of their biological behaviour constitutes a critical determinant for advancing the healing cascade. SC-NVs, as natural carriers of bioactive molecules, can orchestrate the repair process through the delivery of functional proteins and nucleic acids. For example, they contain a high concentration of platelet-derived growth factor, epidermal growth factor and fibroblast growth factor, which drives fibroblast differentiation into myofibroblasts. This enhances contractility and matrix secretion while promoting epidermal cell migration and proliferation, thereby accelerating re-epithelialization.[137,138] Wang *et al.* engineered a multifunctional hydrogel incorporating magnesium-doped bioactive glass-induced nanovesicle clusters to promote diabetic wound healing through the enhanced intracellular delivery of extracellular nanovesicles. Experiments confirmed that treatment with MSC-derived small extracellular nanovesicles (sEVs)

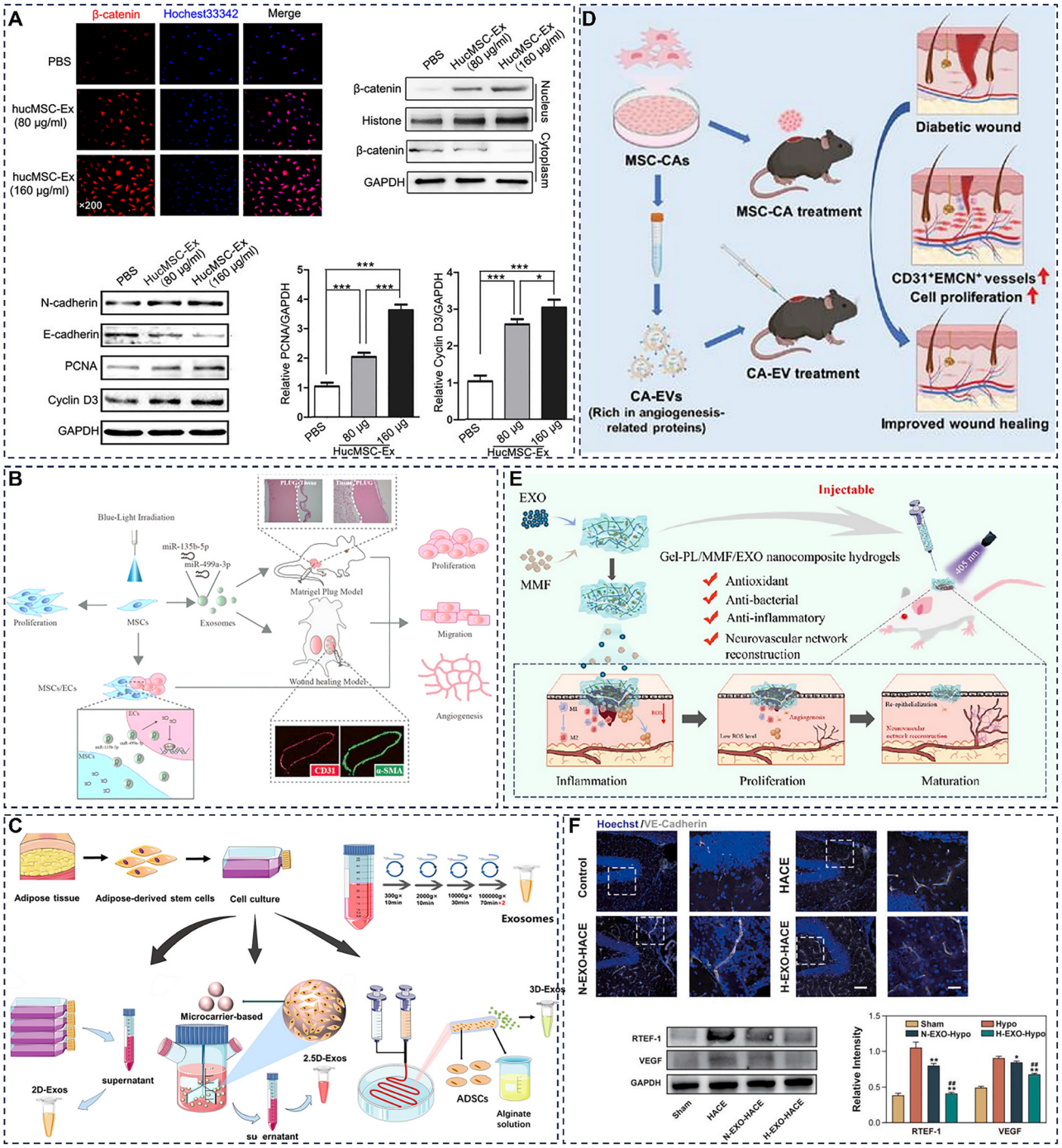

Fig. 6 (A) HucMSC-Ex prompted angiogenesis by activating Wnt/β-catenin signaling. Reproduced with permission from ref. 121. Copyright 2015 John Wiley and Sons Ltd. (B) Blue (455 nm) light illumination enhances the hUC-MSC exosomes proangiogenic ability. Reproduced with permission from ref. 122. Copyright 2019 BioMed Central. (C) Schematic diagram of different processes to culture ADMSCs for exosomes extraction. Reproduced with permission from ref. 124. Copyright 2024 Chinese Society for Biomaterials. (D) MSC aggregation released extracellular vesicles induce CD31 + EMCN + vessels in skin regeneration. Reproduced with permission from ref. 127. Copyright 2023 Wiley. (E) Schematic depiction of the wound healing process. Reproduced with permission from ref. 131. Copyright 2025 American Chemical Society. (F) The effect of H-EXO on cerebral vessels in HACE mice. Reproduced with permission from ref. 132. Copyright 2025 Elsevier.

significantly increased the proliferation, migratory and invasive abilities of L929 fibroblasts and HUVECs, indicating that sEVs retain the pro-reparative capacity of their parental stem cells (Fig. 7A).[139] In addition to the direct use of natural nanovesicles, preconditioning stem cells to augment vesicular function represents a complementary therapeutic strategy. Calcium silicate (CS) could directly promote the proliferation and differentiation of fibroblasts and endothelial cells, while

releasing calcium and silicon ions to establish a permissive microenvironment for stimulating nanovesicle secretion.[140] Lin *et al.* engineered a sustained-release therapeutic system for diabetic wound healing by incorporating collagen hydrogel with CS-stimulated Exos derived from ADSC-derived Exos (CSEVs). Compared with unstimulated EV-loaded collagen, CSEV-loaded collagen enhanced cell proliferation and migration, thereby accelerating wound re-epithelialisation and organized collagen deposition in a diabetic rabbit model (Fig. 7B).[141] Within the pathological microenvironment of diabetic wounds, sustained hyperglycemic stress promotes the accumulation of senescent repair cells. These cells secrete the SASP, which reduces ECM viscoelasticity, prevents cell migration and disrupts tissue repair, thereby obstructing wound healing.[142] Ding *et al.* used Tβ4-engineered ADSC-derived extracellular nanovesicles to attenuate senescent cell burden through detachable microneedle patches, which promoted diabetic wound healing. ADSCs transduced with Tβ4-overexpressing lentiviral vectors generated EVs that were efficiently internalised by target cells. These EVs activated the PTEN/PI3K/AKT pathway to attenuate cell senescence in HUVECs and HDFs and promote cell proliferation and migration in diabetic wound models (Fig. 7C).[143] The isolation of stem cells from human exfoliated deciduous teeth (SHED) was first reported in 2003.[144] These stem cells have an inherent self-renewal capacity and are readily accessible, which indicates their potential use in tissue repair. Bastidas *et al.* subsequently reported that nanovesicles derived from SHED effectively enhanced keratinocyte migration and viability while mitigating H_2O_2-induced cellular damage (Fig. 7D).[145]

Traditional wound treatment often addresses antimicrobial therapy and tissue repair as distinct clinical interventions, resulting in the ineffective coordination of inflammation control and tissue regeneration. To overcome this limitation, researchers have focused on integrating antimicrobial effects with pro-proliferative mechanisms. By concurrently suppressing bacterial infection and stimulating cell proliferation, this strategy aims to shorten the inflammatory-to-proliferative transition, thus augmenting overall wound healing efficacy. For instance, Zeng *et al.* encapsulated the novel bacteria-responsive type I photosensitizer NBS-PB within hUC-derived nanovesicles (hUC-EVs). Specifically, H_2O_2 triggers NBS-PB to generate the photosensitizer NBS, thus reducing excessive inflammation by eliminating infection. hUC-EVs attenuated the immune response and enhanced cell proliferation and migration, thereby accelerating refractory wound healing. This engineered, activatable, biocompatible nanovesicle system (EVs@NBS-PB) achieved targeted bacterial eradication and modulated the wound microenvironment to accelerate healing of refractory wounds (Fig. 7E).[146] He *et al.* developed a dual-network hydrogel spray system that incorporates stem cell-derived sEVs for the treatment of infected skin wounds. The results indicated that poly-ε-lysine-mediated bactericidal activity, combined with sEV-facilitated cell proliferation and migration, significantly accelerated wound healing and achieved 92.63% closure after 14 days of treatment. This study supports the development of more convenient sEV-based formulations for accelerating wound healing (Fig. 7F).[147]

3.5. SC-NVs reduce scar formation

Refractory wound healing frequently culminates in pathological scarring, which is characterised by aberrant granulation tissue transformation and excessive collagen deposition mediated by the TGF-β/SMAD2 signalling pathways. This results in rigid, itchy and painful HSs or keloids.[148,149] Wang *et al.* showed that ADSC-Exos significantly promote ECM reconstruction during cutaneous wound repair. This was achieved by regulating the ratios of collagen type III to type I, TGF-β3 to TGF-β1 and matrix metalloproteinase-3 (MMP3) to TIMP1 as well as by regulating fibroblast differentiation to mitigate scar formation (Fig. 8A).[150] Li *et al.* further demonstrated the anti-fibrotic efficacy of ADSC-Exos. ADSC-Exos accelerated wound healing in animal models by downregulating Col1/Col3/α-SMA/IL-17RA/p-SMAD2/3 and upregulating SIP1 expression, which reduced collagen deposition and mitigated hypertrophic scar fibrosis (Fig. 8B).[151] MSC-derived nanovesicles enriched with miRNAs, such as miR21, miR-23a, miR-125b and miR-145, can prevent scar formation by inhibiting the development of myofibroblasts through the suppression of excessive α-smooth muscle actin and collagen deposition associated with the TGF-β/SMAD2 signalling pathway. MicroRNA-125b-5p (miR-125b-5p), which is highly enriched in ADSC-derived exosomes, directly binds to the 3′ untranslated region (3′UTR) of Smad2, thereby inhibiting fibrosis in myofibroblasts and ameliorating hypertrophic scarring.[152] Zhao *et al.* used MSC-derived Exos to deliver miR-138-5p, which targets silent information regulator 1 (SIRT1). They demonstrated that miR-138-5p inhibited the proliferation and migration of HSF cells, and suppressed the expression of NF-κB, alpha smooth muscle actin (α-SMA) and TGF-β1, thereby ameliorating pathological scarring (Fig. 8C).[153] To recapitulate the temporal process of natural wound healing, Shen *et al.* developed a bilayer thiolated alginate/PEG diacrylate (BSSPD) hydrogel that promoted rapid and scarless wound healing by sequential release of sEVs. The sEVs secreted by BMSCs (B-sEVs) were released from the lower layer of the hydrogels to promote collagen deposition by accelerating fibroblast proliferation and migration during the early inflammation and proliferation phases. Moreover, the sEVs secreted by miR-29b-3p-enriched BMSCs were released from the upper layer of the hydrogels to suppress excessive capillary proliferation and collagen deposition during the late proliferation and maturation phases. In a full-thickness skin defect model of rat and rabbit ears, the tissues in the groups treated with sEV-loaded BSSPD for sequential release (SR-sEVs@BSSPD) exhibited more regular collagen arrangement and a lower volume of hyperplastic scar tissue than the other groups (Fig. 8D).[154] Epidermal stem cells (ESCs) have an inherent ability to proliferate and differentiate into various epidermal lineages, demonstrating superior efficiency in wound healing and scar reduction compared with other stem cell types. Zhen *et al.* used next-generation sequencing and multiplex CRISPR/Cas9 to show that ESC-EVs reduced Zinc Finger E-Box Binding

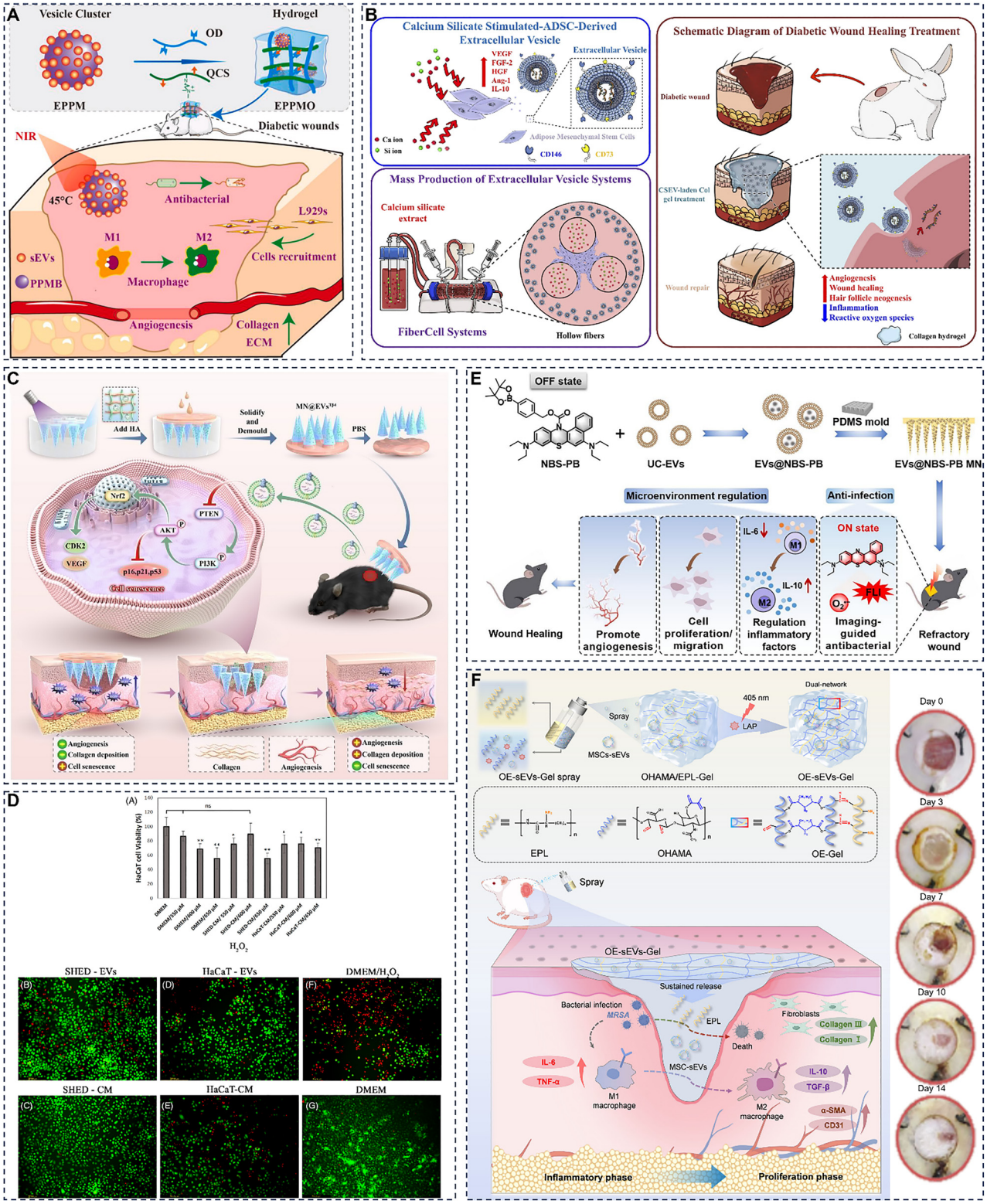

Fig. 7 (A) Schematic diagram of EPPMO hydrogel properties. Reproduced with permission from ref. 139. Copyright 2025 Elsevier. (B) Schematic representation of the therapeutic application of CSEV for diabetic wound healing. Reproduced with permission from ref. 141. Copyright 2025 Springer. (C) Schematic diagram illustrating application of Tβ4-overexpressing EV-loaded microneedle patches for facilitating wound treatment. Reproduced with permission from ref. 143. Copyright 2025 Wiley. (D) MTT assay of HaCaT cells submitted to different H_2O_2 concentrations and then treated with different treatments. Reproduced with permission from ref. 145. Copyright 2023 Wiley. (E) Schematic illustration of EVs@NBS-PB MNs for synergetic phototheranostics and microenvironment regulation in hypoxia diabetic wounds. Reproduced with permission from ref. 146. Copyright 2025 Elsevier. (F) Schematic illustration of OE-sEVs-Gel-mediated wound healing. Reproduced with permission from ref. 147. Copyright 2025 Wiley.

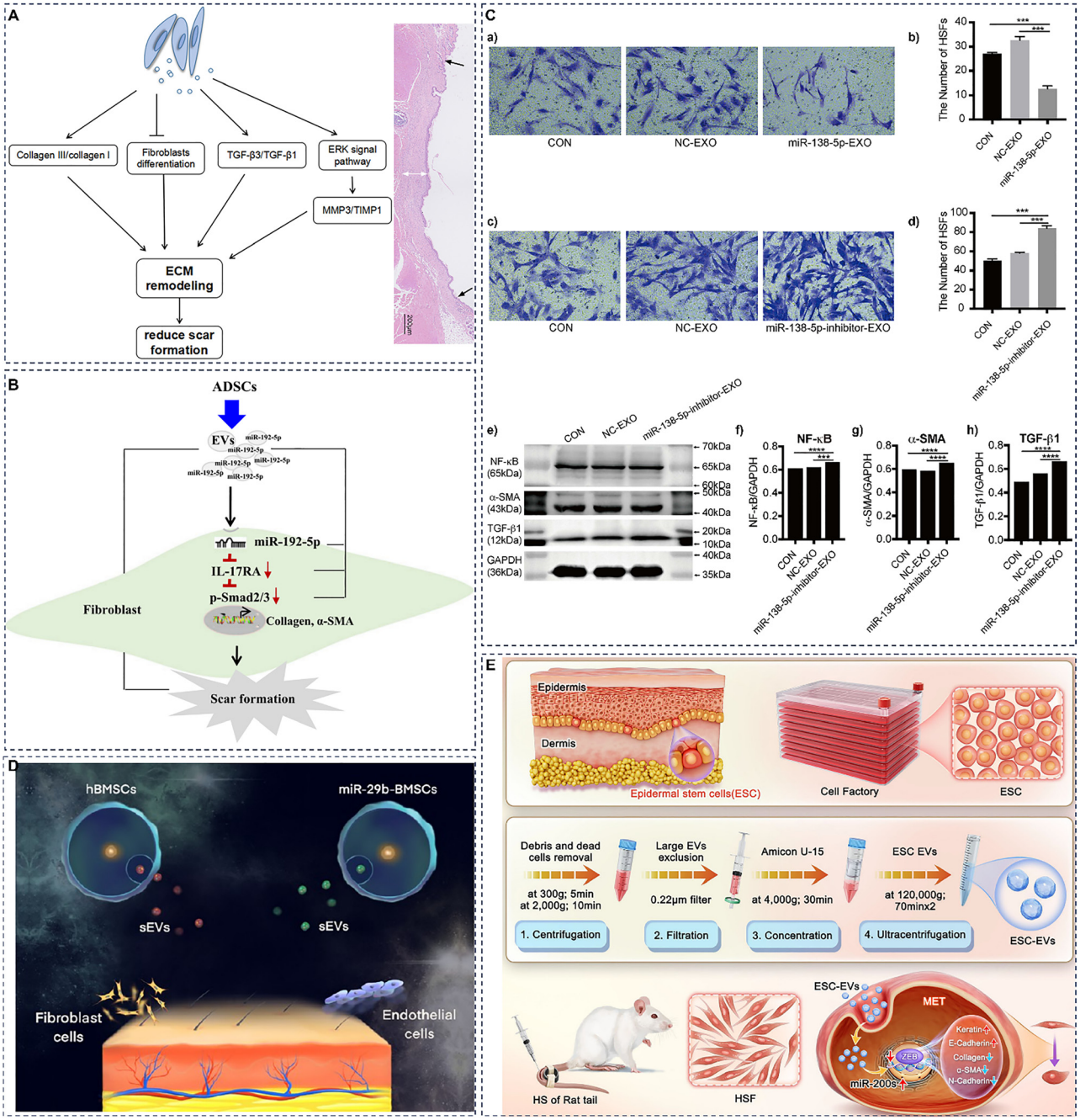

Fig. 8 (A) ASC-derived exosomes contributed to regulating ECM reconstruction and reducing scar formation. Reproduced with permission from ref. 150. Copyright 2017 Springer Nature. (B) The effect of ADSC-Exo on Smad pathway in HSFs. Reproduced with permission from ref. 151. Copyright 2021 BioMed Central. (C) The effect of miR-138-5p on protein expression of HSFs. Reproduced with permission from ref. 153. Copyright 2022 Dove Medical Press Limited. (D) Sequential release of small extracellular vesicles from bilayered hydrogels for scarless wound healing. Reproduced with permission from ref. 154. Copyright 2021 American Chemical Society. (E) Schematic illustration of ESC-EVs alleviating HS. Reproduced with permission from ref. 155. Copyright 2025 Wiley.

Homeobox 1 (ZEB1) and ZEB12 expression *via* miR-200s, thereby inhibiting HSF contractile capacity and mitigating hypertrophic scar formation (Fig. 8E).[155] Zhao *et al.* demonstrated that EpiSC-EVs enriched in miR-203a-3p mediate myofibroblast dedifferentiation by suppressing PIK3CA expression and inhibiting the PI3K/AKT/mTOR pathway, ultimately attenuating excessive scarring.[156]

4. Responsive hydrogels based on SC-NVs for wound treatment

Refractory wounds exhibit an impaired self-repair capacity, which is attributed to their complex pathological microenvironment, characterised by pH dysregulation, oxidative stress, abnormal enzymatic activity, and pathogenic infection.[157,158]

An ideal wound dressing should function as both a protective barrier and a platform for localised drug delivery with stimulus-responsive properties to modulate the microenvironment, thereby accelerating healing.[159] As highly hydrophilic three-dimensional polymer networks, hydrogels exhibit excellent biocompatibility, degradability, porous architecture and tunable mechanical properties, making them an ideal platform for loading SC-NVs.[29,160] Common strategies for encapsulating exosomes into hydrogels include mix–cross, *in situ* gelation and physical incorporation.[161,162] In the mix–cross method, SC-NVs are blended with hydrogel polymer chains and then crosslinked using crosslinking agents or external triggers. This method is straightforward to perform and facilitates the uniform distribution of the SC-NVs. *In situ* gelation is typically achieved using a dual-chamber syringe, with one chamber containing polymer chains and SC-NVs and the other containing a crosslinker. Upon injection, the gel forms rapidly at the wound site. The exceptional conformability enables it to adhere tightly to irregular wound surfaces. The physical incorporation technique exploits the swelling and shrinkage behaviour of smart hydrogels. These hydrogels form expanded network structures in aqueous environments, but undergo collapse and phase separation when exposed to low polarity solvents. However, the pore size of the hydrogel must be tunable and exceed the dimensions of the target exosomes to allow them to infiltrate the polymer matrix.[163] Furthermore, hydrogels can reversibly alter their physicochemical properties in response to external stimuli, thereby enabling precisely controlled release kinetics (Fig. 9).[164] This section discussed the therapeutic potential of stimulus responsive hydrogels for refractory wound repair, with a particular emphasis on the synergistic integration with SC-NV therapies. In particular, it addressed the underlying mechanisms and therapeutic prospects of such composite systems for improving wound healing outcomes.

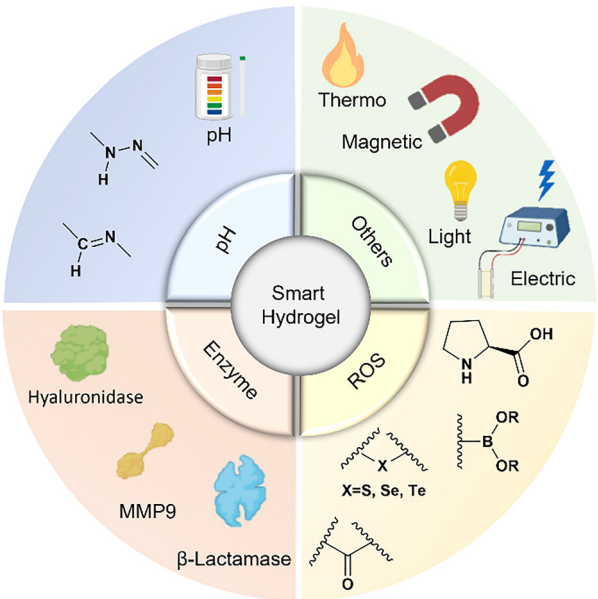

Fig. 9 Schematic diagram of a stimulus-responsive hydrogel as an intelligent drug delivery platform in the biomedical field (created with BioRender.com).

4.1. pH-responsive hydrogels

pH is an important dynamic indicator during wound healing, directly reflecting tissue regeneration status and infection severity.[165,166] Intact, healthy skin maintains a mildly acidic microenvironment (pH 4–6).[167] This mildly acidic nature is essential for skin barrier function, effectively inhibiting colonisation and proliferation of pathogenic microorganisms, such as *S. aureus* and Malassezia spp., thus reducing the risk of infection.[168] Following skin barrier disruption, the wound microenvironment exhibits characteristic pH fluctuations. During the initial injury phase, tissue ischaemia and bacterial metabolism generate a lower pH.[169] During subsequent healing stages, aerobic metabolism replaces glycolysis and gradually increases the pH from acidic towards physiological levels.[170] Persistent infection induces an alkaline pH shift through ammonia production by *Pseudomonas aeruginosa* and other bacteria, along with tissue necrosis. This alkalisation not only compromises local antimicrobial defence but also promotes bacterial biofilm formation, delays epithelial regeneration and severely impairs healing.[171] To address the pathological pH dynamics in refractory wounds, researchers have engineered intelligent pH-responsive hydrogels that enable on-demand degradation and precise drug release. This was achieved by incorporating either acid-responsive bonding structures (*e.g.* amino, imine and carboxyl groups) or deprotonated structures (*e.g.* carboxyl groups) into drug-loaded hydrogels.[172,173] Chen *et al.* engineered a multifunctional PF127/CMCS/GA/EV hydrogel system for the treatment of infected wounds, incorporating extracellular nanovesicles derived from hUCMSCs. In this system, PF127-$(CHO)_2$ aldehyde groups crosslink with the CMCS amino groups through Schiff base bonds, conferring excellent pH sensitivity. This pH sensitivity enables controlled EV release within the acidic infected wound milieu, thereby promoting angiogenesis, cell migration, proliferation and reepithelialisation. Moreover, the incorporation of gallic acid confers antibacterial, anti-inflammatory and anti-oxidant properties. Combined with EVs, this formulation significantly accelerated wound healing in a MRSA-infected mouse full-thickness skin defect model (Fig. 10A).[174] Tang *et al.* designed a GDHP hydrogel specifically tailored to the diabetic wound microenvironment. The hydrogel was synthesised from dopamine-grafted gelatin and phenylboronic acid-grafted hyaluronic acid. The phenylboronic acid ester bonds undergo hydrolysis in response to the acidic or high glucose wound environment to deliver huc-MSC-Exos and ciprofloxacin hydrochloride. This dual-delivery system modulated local glucose homeostasis, scavenged ROS, suppressed inflammation, promoted keratinocyte migration and ultimately improved the wound microenvironment. This strategy offered a novel approach for microenvironmental regulation in diabetic nonhealing wounds (Fig. 10B).[175] Because of the abundant amino groups, the electrostatic interactions of chitosan with other molecules are pH-dependent.[176] Yuan *et al.* developed a thermostable chitosan scaffold (T-CS)

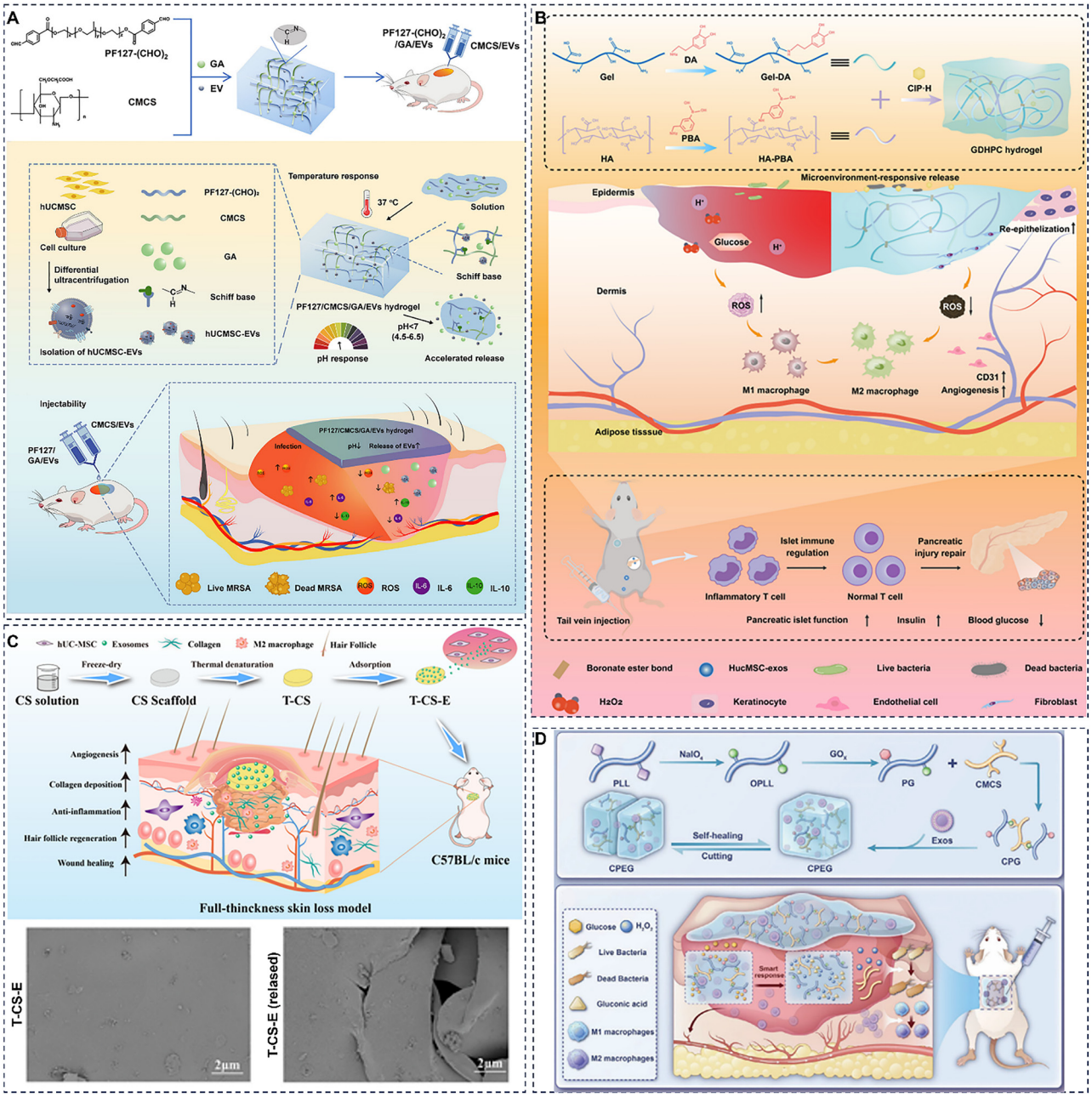

Fig. 10 (A) Schematic illustration of PF127/CMCS/GA/EV hydrogels promoting wound healing. Reproduced with permission from ref. 174. Copyright 2025 Wiley. (B) Schematic illustration of multifunctional GDHPC hydrogels combined with hucMSC-exos for repair of diabetic wounds. Reproduced with permission from ref. 175. Copyright 2025 Elsevier. (C) Schematic diagram of the mechanism of T-CS-E in promoting regenerative wound healing. Reproduced with permission from ref. 177. Copyright 2025 Elsevier. (D) Schematic diagram of CPEG hydrogels for the repair of diabetic wounds. Reproduced with permission from ref. 178. Copyright 2024 Wiley.

that enables the pH dependent capture and controlled release of hUC-MSC Exos. This scaffold captures hUC-MSC Exos in acidic environments and sustainably releases them under alkaline or neutral conditions, thereby promoting cell proliferation, reepithelialisation and angiogenesis to enhance full-thickness skin wound healing (Fig. 10C).[177] Yang *et al.* incorporated SC-NVs into a self-healing OPLL/CMCS hydrogel to improve the diabetic wound microenvironment and accelerate healing. The Schiff base bonds within the hydrogel undergo rapid hydrolysis under acidic conditions, triggering Exos release that accelerated healing through antimicrobial, pro-angiogenic and anti-inflammatory effects (Fig. 10D).[178] Although pH-responsive hydrogels enable intelligent drug release by monitoring real-time fluctuations in wound pH, a single pH-responsive strategy is always insufficient to accommodate all stages of refractory wounds. Healthy skin maintains a mildly acidic environment (pH 4–6), which rapidly increases to nearly pH 7.4 following microvascular leakage and plasma exudation, creating an

environment favourable for bacterial colonisation. Subsequently, local ischaemia induces anaerobic glycolysis and lactate accumulation, which temporarily lowers the pH. During the remodelling phase, pH gradually rises again. Concurrently, bacterial infection and biofilm formation introduce further pH variability with considerable heterogeneity between patients. Consequently, static response mechanisms based on a single fixed trigger threshold are inadequate for such dynamic microenvironmental conditions, and fail to meet the personalized treatment requirements of diverse refractory wounds. Advances toward multifunctional designs will enable precision treatment platforms tailored to heterogeneous wound microenvironments, accelerating the clinical translation of these materials and the paradigm shift in the management of refractory wounds.

4.2. Enzyme-responsive hydrogels

The wound healing process is characterised by dynamic temporal changes in multiple hydrolases and proteases, whose expression and activity are precisely regulated across the inflammatory, proliferative and remodelling phases. These enzymes directly affect several important processes, including cell migration, ECM remodelling, inflammatory responses and pathogen clearance.[179,180] This highly ordered and stage specific enzyme expression pattern provides targets for developing stimulus-responsive drug delivery systems. Leveraging their high substrate specificity and catalytic efficiency, enzyme-responsive delivery systems enable precise, controlled drug release within complex wound microenvironments, thereby demonstrating significant therapeutic potential. Of these, hyaluronidase is a key enzyme secreted by wound pathogens, which has been extensively employed in the construction of stimulus-responsive drug delivery systems.[181] Researchers have exploited its specific hyaluronic acid-cleaving activity to design hydrogel carriers that degrade following enzyme activation at infection sites. When applied to infected wounds, locally enriched hyaluronidase efficiently hydrolyses the gel matrix, thereby enabling targeted drug delivery.[71] For example, Yu *et al.* developed an injectable hyaluronic acid hydrogel for loading MSC-Exos. In a hyaluronidase-rich wound environment, this hydrogel promoted wound closure, angiogenesis, and tissue regeneration through sustained Exos release (Fig. 11A).[182] Considering the dynamic nature of wound microenvironments, Zhao *et al.* further engineered a dual-layer hydrogel (Dual-Gel) responsive to burn wound microenvironments. The inner layer (Gel 2) responded to bacterial hyaluronidase by delivering photosensitiser-functionalised adipose-derived SC-NVs that generate ROS upon light irradiation to eliminate bacteria. The outer layer (Gel 1) continuously scavenged excess ROS at the wound site to accelerate tissue regeneration. Concurrently, released SC-NVs also delivered bioactive factors that mobilised adjacent tissues, thereby regulating inflammation, promoting cell proliferation, migration, and angiogenesis (Fig. 11B).[183] Clinical observations indicated that refractory wounds are frequently covered by dense eschar or necrotic tissue, which prevent the penetration of traditional ointments.[184,185] Ma *et al.* engineered a core–shell hyaluronic acid microneedle patch encapsulating iron-modified mesenchymal SC-NVs and polydopamine nanoparticles within the needle tips. Upon microneedle penetration into the dermis, the gradual degradation of the hyaluronic acid needle tip facilitated the sustained release of therapeutic cargo at the wound site. This approach demonstrated robust anti-inflammatory, antioxidant, and pro-angiogenic effects, significantly accelerating wound healing in diabetic ulcer models (Fig. 11C).[186]

During wound healing, the dynamic equilibrium of proteases is important for successful repair. Persistently elevated expression of matrix metalloproteinases (matrix metalloproteinase-9, MMP-9) constitutes a key pathological indicator of a dysregulated microenvironmental. Aberrant activation of these proteases degrades nascent ECM and growth factors, thereby disrupting granulation tissue formation and epithelialisation, which is a pathological hallmark of delayed wound healing.[187,188] To ameliorate this cascade, MMP9-responsive hydrogel-based drug delivery systems have been used to augment wound healing kinetics. Meng *et al.* developed a stimulus-responsive hydrogel engineered to release M2 macrophage-derived Exos (M2-Exos) in response to pathological MMP-9 signals within the inflammatory microenvironment. These M2-Exos promote the polarisation of macrophages from the M1 to the M2 phenotype, thus facilitating the inflammatory-to-proliferative transition and accelerating diabetic wound healing (Fig. 11D).[189] Wang *et al.* developed a nanozyme hydrogel capable of dynamically scavenging ROS at the wound site in response to MMP-9 fluctuations. Through adaptive immune regulatory mechanisms, this system promoted epithelial regeneration, angiogenesis, collagen deposition and significantly accelerated diabetic wound healing (Fig. 11E).[190] Therefore, the integration of responsive hydrogels with SC-NVs, constitutes a promising strategy for the development of advanced therapeutic interventions. Enzyme-responsive hydrogels can precisely recognise dysregulated enzymes (*e.g.*, MMP9) overexpressed in refractory wounds, enabling on-demand targeted therapy while minimising off-target effects on healthy tissue. However, enzymatic activity exhibits significant spatial and temporal heterogeneity across healing phases, individual patients, and wound microenvironments, complicating the design of appropriate response thresholds. Moreover, the integration of enzyme-cleavable moieties substantially increases manufacturing complexity and costs. Furthermore, enzymatic kinetics are susceptible to environmental disturbances and exhibit inconsistent reaction rates, making them unsuitable for time-critical interventions during acute exacerbations. Personalised formulations tailored to patient-specific enzyme profiles could offer distinct clinical advantages in chronic wound management. Nevertheless, most relevant studies remain at the preclinical stage, requiring comprehensive validation before clinical translation.

4.3. ROS-responsive hydrogels

ROS are highly reactive oxygen-containing molecules that are generated during oxygen metabolism in living organisms. They consist of singlet oxygen ($^1O_2$), hydrogen peroxide (H_2O_2),

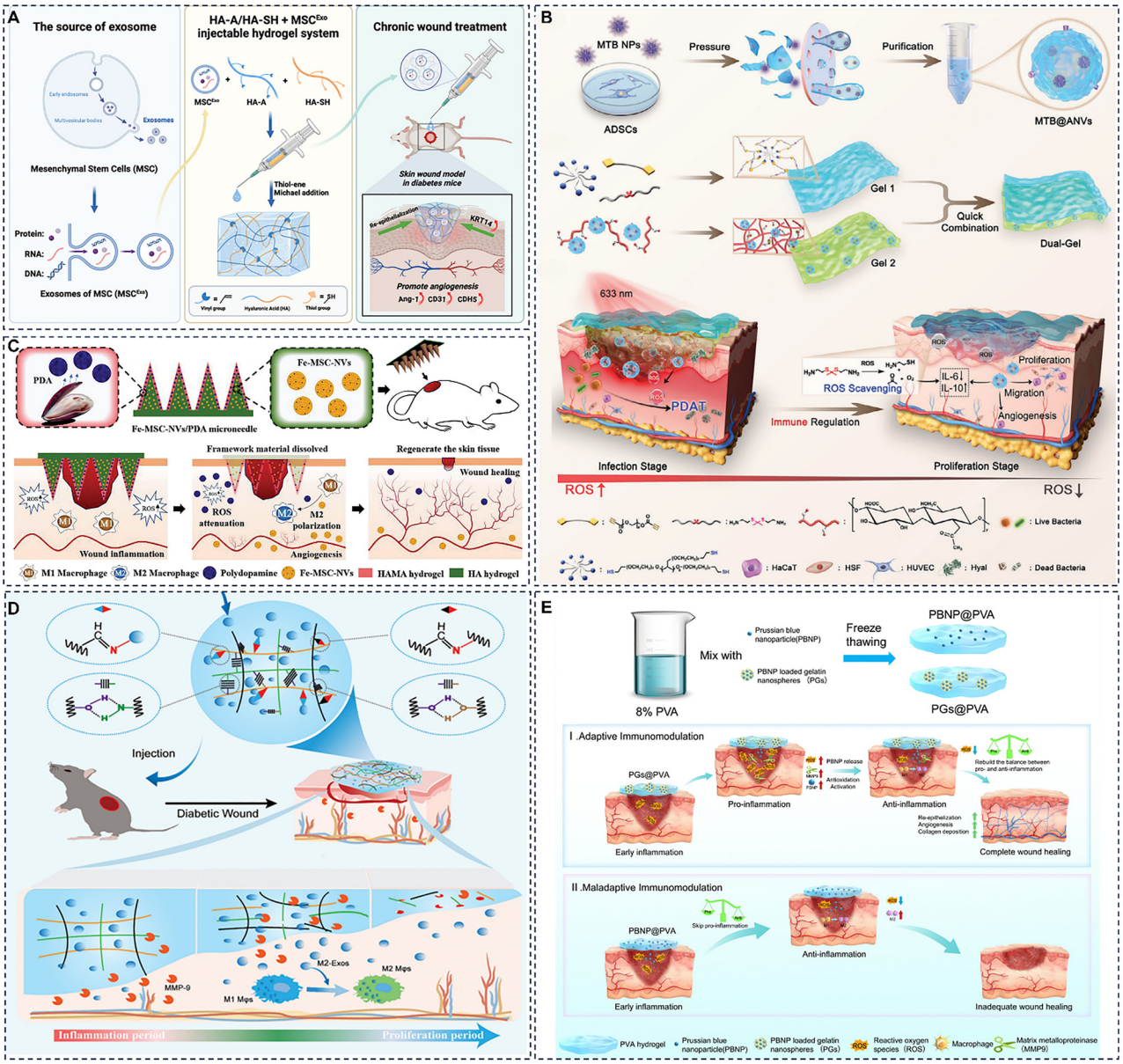

Fig. 11 (A) Application diagram of HA-A/HA-SH@Exo hydrogels. Reproduced with permission from ref. 182. Copyright 2025 Elsevier. (B) Schematic diagram of the burn wound healing process programmed by Dual-Gel. Reproduced with permission from ref. 183. Copyright 2024 Wiley. (C) Schematic illustrations of an Fe-MSC-NVs/PDA MN patch for diabetic wound healing. Reproduced with permission from ref. 186. Copyright 2022 Wiley. (D) Schematic diagram of Exo@MRH facilitating diabetic wound healing. Reproduced with permission from ref. 189. Copyright 2025 Wiley. (E) Schematic diagram of the hydrogels promoting wound healing in different modes. Reproduced with permission from ref. 190. Copyright 2025 The Royal Society of Chemistry.

superoxide anions ($O_2^{\bullet -}$) and hydroxyl radicals ($^{\bullet}OH$).[191] Under physiological conditions, moderate ROS concentrations are required for the recruitment of immune cells, clearance of pathogens and tissue repair.[192] However, in refractory wounds, persistent local ischaemia hypoxia, infection, and inflammatory responses drive excessive ROS accumulation. This accumulation leads to severe oxidative stress and persistent activation of proinflammatory signalling pathways, such as NF-κB and MAPK. The resulting oxidative damage causes DNA injury and protein dysfunction, ultimately disrupting wound healing.[193,194] ROS responsive hydrogels enable targeted drug release through ROS-mediated scaffold degradation and actively scavenge excess ROS, thus mitigating oxidative stress injury.[195] Multifunctional hydrogel systems integrating dual ROS scavenging and drug delivery capabilities have been developed recently, which showed significant therapeutic efficacy in various refractory wound models. Jing *et al.* engineered a ROS/glucose dual-responsive hydrogel based on phenylboronic acid-modified lignin gum (LG-PBA) and polyvinyl alcohol (PVA). This system enabled triggered release of ADSC-derived Exos and chlorogenic acid following exposure to elevated ROS or glucose levels. By restoring mitochondrial electron transport chain

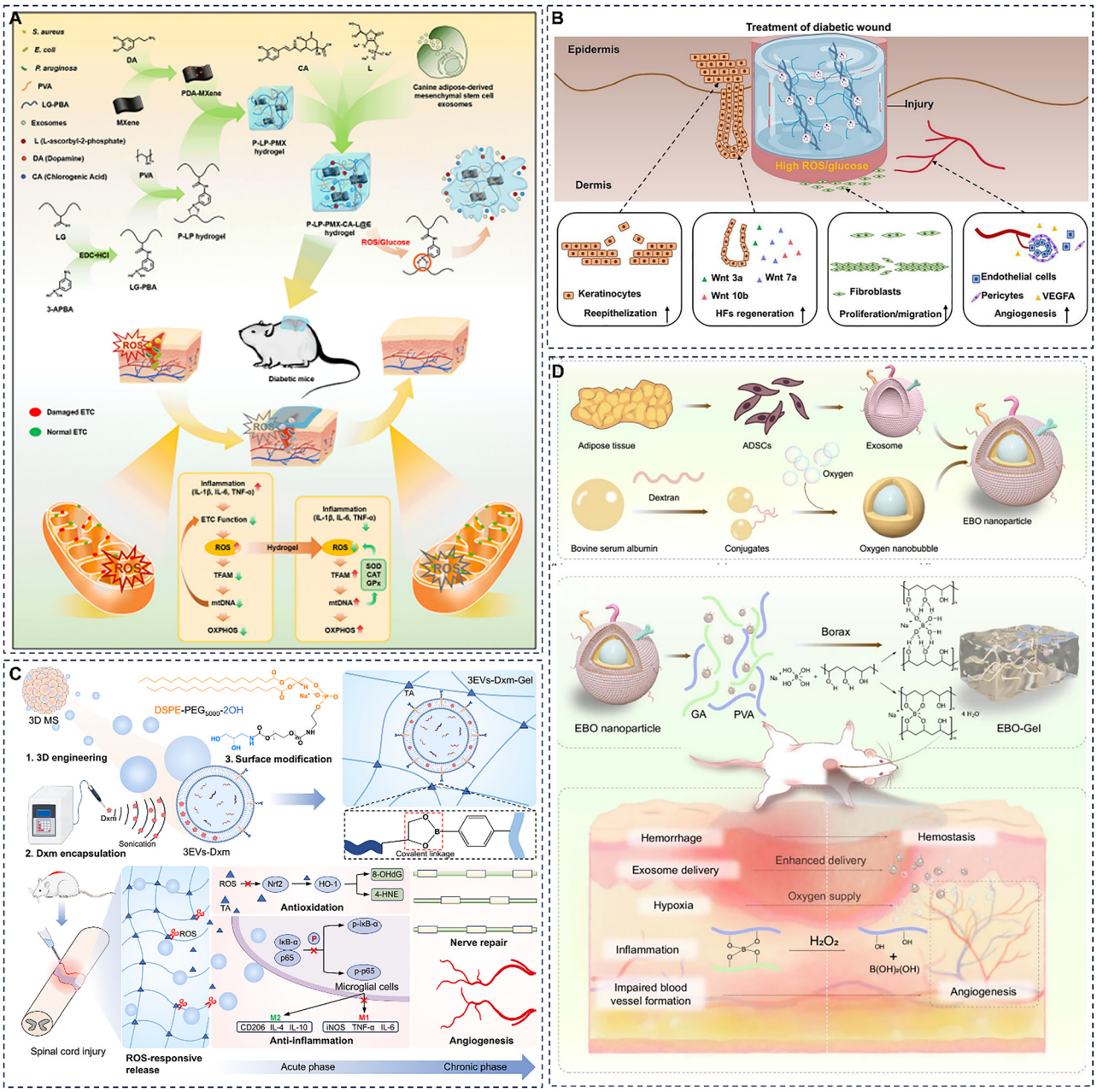

Fig. 12 (A) The mechanism of hydrogels for wound healing. Reproduced with permission from ref. 196. Copyright 2024 Elsevier. (B) Controlled release of MSC-derived nanovesicles through ROS-responsive hydrogels accelerates diabetic wound healing. Reproduced with permission from ref. 197. Copyright 2024 Elsevier. (C) Illustration of the therapeutic mechanism of 3EVs-Dxm-Gel in SCI treatment. Reproduced with permission from ref. 198. Copyright 2025 American Association for the Advancement of Science. (D) Enhanced wound healing by EBO-Gel. Reproduced with permission from ref. 199. Copyright 2024 Springer Nature.

function, this system effectively attenuated oxidative stress and inflammation, thereby promoting skin wound healing in type 1 diabetic mice (Fig. 12A).[196] Du *et al.* developed a glucose and ROS responsive exosome hydrogel (Exo-Gel), which significantly accelerated wound healing in a diabetic wound model by promoting epithelialisation, dermal reconstruction, hair follicle formation and angiogenesis (Fig. 12B).[197] In addition to the structural design of responsive hydrogels, modification of the delivery vehicle itself is an emerging strategy for enhancing therapeutic efficacy. Cao *et al.* increased the bioactivity of extracellular nanovesicles (EVs) using 3D culture and drug encapsulation, subsequently loading these engineered EVs into ROS-responsive hydrogels for controlled release. In spinal cord injury models, the 3EVs-Dxm-Gel system ameliorated oxidative damage and neuroinflammation, and promoted neurorepair and angiogenesis (Fig. 12C).[198] To address the challenges of tissue haemorrhage and hypoxic microenvironments during wound healing, Han *et al.*

developed a tissue-adhesive PVA/GA composite hydrogel, which provided effective hemostasis for irregular, bleeding wounds, while enhancing Exos delivery efficiency and alleviating tissue hypoxia through embedded oxygen-loaded nanobubbles carrying Exos. The EBO-Gel system efficiently scavenged ROS and improved oxygen supply, thereby accelerating wound healing and significantly reducing the risk of hypertrophic scar formation. This represents a novel strategy for scar prevention and management (Fig. 12D).[199] ROS-responsive hydrogels offer a novel therapeutic strategy for chronic wounds *via* their bifunctional capability to simultaneously scavenge ROS and trigger drug release. In clinical settings, refractory wounds are often characterised by polymicrobial colonisation and pathological oxidative stress. Through bidirectional modulation, these systems can photodynamically generate exogenous ROS to eliminate pathogens during the infectious phase, while subsequently scavenging endogenous ROS during the inflammatory resolution phase to attenuate oxidative stress, thereby synergistically promoting wound healing. Nevertheless, unregulated ROS generation during antimicrobial photodynamic therapy may result in collateral tissue damage. Furthermore, ROS-labile moieties (*e.g.*, boronate ester linkages) have limited hydrolytic stability under ambient conditions, posing challenges for long-term storage and terminal sterilisation protocols. Future research should focus on the incorporation of bioactive phytocompounds with intrinsic antioxidant capacity. This approach would concurrently enhance physicochemical stability and clinical translatability while optimising bidirectional ROS modulation.

4.4. Physically responsive hydrogels

In addition to biological stimuli, physically responsive hydrogels represent another effective strategy for accelerating wound healing. This approach primarily uses external stimuli such as temperature, light, magnetism, and electricity to achieve on demand drug release and temporal regulation of the wound microenvironment. Zheng *et al.* incorporated VEGF- and TFEB-loaded engineered nanovesicles (VEGF/TFEB@EVs) into thermo-responsive hydrogels, thereby enhancing the release of the nanovesicles, improving blood flow recovery *in vivo*, mitigating muscle damage, and restoring limb function in critical limb ischaemia (CLI) models.[200] Magnetically regulated systems offer significant advantages for the treatment of deep wounds due to their superior tissue penetration and remote controllability. Xia *et al.* developed a superparamagnetic multifunctional neural scaffold that can generate EVs on demand. This system acted as a mechanical stimulation platform, applying micro/nanoscale forces to Schwann cells (SCs) encapsulated within magnetic hydrogels to generate nanovesicles *in situ* for remote-controlled peripheral nerve repair.[201] Huang *et al.* developed a photo- and magneto-responsive drug delivery hydrogel for the healing of deep chronic wounds. Exposure to near-infrared light or alternating magnetic fields significantly increases the temperature of MNPs@MXene, causing the hydrogel matrix to contract. This mechanism precisely controlled the release of AgNPs for the eradication of bacteria adhering to deep wound tissues.[202] Notably, electrotherapy has emerged as an innovative treatment for chronic, difficult-to-heal wounds. The inherent conductivity of the skin facilitates the transmission of microcurrent to promote keratinocyte migration, enhance epithelial regeneration, guide angiogenesis and modulate growth factor expression, thereby accelerating the healing process. Wang *et al.* developed an ultrasound-responsive conductive gel (CGGP) that operated *via* interfacial ion/electron transfer for electrotherapy of diabetic wounds. This CGGP promoted neurotrophic factor secretion, angiogenesis and fibroblast migration, and facilitated local nerve regeneration, vascular formation and matrix remodeling in a diabetic rat model.[203] This strategy employs external stimuli to precisely modulate therapy, thus bypassing microenvironmental heterogeneity and variability between patients. Moreover, some stimuli also promote cell proliferation. However, its clinical application heavily relies on specialised equipment, increasing procedural complexity and economic burden while restricting accessibility in primary care or resource-limited settings. Furthermore, these interventions require device-specific regulatory pathways, introducing additional barriers to clinical translation. Emerging integration with intelligent monitoring platforms is expected to enhance clinical translatability.

5. Summary and prospects

The clinical management of refractory wounds is significantly challenging. Examining their repair mechanisms and developing novel therapeutic strategies are major areas of focus for biomedical researchers. SC-EVs have recently emerged as a promising therapeutic modality with biological activity across multiple repair pathways. They exhibit regenerative capabilities comparable to stem cells and offer several advantages, including low immunogenicity, minimal tumorigenic risk, stable physicochemical properties, and facile storage and transport. These nanovesicles are important mediators of intercellular communication and tissue regeneration, demonstrating multifunctional properties: (1) infection control, where they deliver antimicrobial agents locally, thus enhancing local anti-infective capacity. (2) Inflammation regulation, through which they enrich miR-146a and IL-10 promoting macrophage polarisation from pro-inflammatory M1 to reparative M2 phenotypes, thus mitigating excessive inflammatory responses. (3) Angiogenesis, in which nanovesicles enriched with pro-angiogenic factors, such as VEGF and miR-126, activate endothelial cells to promote neovascularization. (4) Proliferation and re-epithelialisation, where they deliver active components, including miRNAs and proteins, to activate key signalling pathways (PI3K/Akt and Wnt/β-catenin), thereby driving fibroblast and keratinocyte migration and proliferation to accelerate tissue remodelling. (4) Suppress scar formation by modulating fibroblast function and ECM remodelling. Although SC-NVs demonstrate promising therapeutic potential in refractory wound healing, their clinical use is limited by stability issues. Unlike liposomes or polymeric nanoparticles, SC-NVs have a

phospholipid bilayer membrane that is susceptible to damage from freezing and thawing cycles, enzymatic degradation, and pH fluctuations, which can cause membrane destabilization, cargo leakage, or irreversible aggregation. Even when stored at −80 °C storage, activity loss can exceed 50% over a 26-week period.

Hydrogels are ideal carrier systems for achieving the sustained, stable delivery of SC-NVs at the wound site because of their superior biocompatibility, high water retention capacity, tunable mechanical properties and controllable drug release. Their porous architecture and designable cross-linked networks facilitate the on-demand release of SC-NVs in response to microenvironmental stimuli, thus preventing rapid clearance and maintaining local therapeutic concentrations. Nevertheless, during encapsulation *via* physical mixing, sonication, or *in situ* gelation, vesicles are subjected to shear stress, free radical polymerization, or osmotic shock, which may alter the structure of surface proteins on the vesicles, thereby compromising vesicle bioactivity and inherent targeting specificity of the vesicles. Thus, optimal encapsulation strategies must preserve vesicle structural integrity and bioactivity, along with efficient cargo loading and controlled release to maximise the therapeutic efficacy of the integrated platform. Emerging approaches leveraging mild bioorthogonal chemistries or stimuli-responsive phase-change hydrogels also demonstrate considerable potential for mitigating these challenges. This review summarises effective strategies for promoting refractory wound healing by delivering SC-NVs to injury sites using stimulus-responsive hydrogels to significantly increase the retention of nanovesicles and their biological activity at wound sites. These hydrogels respond to multiple wound microenvironmental signals, such as pH fluctuations, enzyme concentration shifts, and ROS levels to adapt the programmed changes in physicochemical properties. This provides novel therapeutic modalities for managing complex, chronically evolving refractory wounds.

Despite promising preclinical applications, several important challenges persist. First, the progression of refractory wounds is characterised by a multi-stage, temporally evolving microenvironment. Existing hydrogel systems show limited adaptability across all phases, which limited their overall therapeutic efficacy. Second, although efforts have focused on integrating dual or multi-response mechanisms to enhance synergistic therapeutic effects, the interactions between different response pathways and their potential off-target biological effects have not been fully characterised. Moreover, multi-responsive hydrogels face inherent challenges including complex structural design, suboptimal degradation kinetics and limited biocompatibility. In addition, as carriers of nanovesicles, hydrogels exhibit limited capacity for precise drug release kinetics, which resulted in premature release or prolonged retention. This instability compromised the therapeutic functionality and repair efficacy of nanovesicles at the wound site. Furthermore, the clinical translation of smart hydrogels faces numerous challenges. Firstly, smart hydrogels are typically fabricated *via* laboratory-scale batch synthesis, wherein production equipment and processes have not yet achieved industrial-scale scaling. This approach is plagued by high costs and faces stringent challenges in achieving terminal sterilization and long-term stable storage. Secondly, significant variations exist among research teams in terms of preparation conditions, characterisation methods and performance evaluation metrics. This results in poor comparability of research outcomes and inconsistent reproducibility from batch to batch, thereby compromising the stability of clinical efficacy. Given its sustained use in clinical treatment, the biocompatibility evaluation of therapeutic agents incorporated within smart hydrogels also requires comprehensive validation. Meanwhile, the lack of standardised evaluation protocols, regulatory consensus, and benchmark models for smart hydrogels presents substantial impediments to product development, quality assurance, and clinical translation. Furthermore, current regulatory frameworks for assessing the safety and efficacy of medical devices are primarily designed for conventional static devices, making them unsuitable for evaluating smart systems with dynamic responsiveness and active therapeutic functions. Therefore, future research requires collaborative efforts across materials science, biology, clinical medicine, production engineering, and regulatory science. Only by systematically overcoming these translational bottlenecks can smart hydrogels be transformed from an exceptional experimental concept into safe, effective, and accessible next-generation wound management dressings in clinical practice.

Despite numerous challenges in optimizing hydrogel performance and achieving clinical translation, stimulus-responsive hydrogels will continue to play a pivotal role in future development of dressings for recalcitrant wounds. This requires advancing these dressings beyond conventional drug delivery towards integrated diagnostic, therapeutic and monitoring systems. Specifically, stimulus-responsive dressings integrating miniature flexible sensor arrays enable continuous, non-invasive monitoring of critical wound microenvironmental parameters, including pH, temperature, humidity, enzyme activity, inflammatory markers, and ROS levels. Using wireless transmission technology, these sensors relay real-time data to healthcare provider interfaces, providing objective metrics for precise healing assessment. Building upon this foundation, artificial intelligence-enabled analysis of multidimensional data streams allows prediction of critical wound status transitions, such as infection onset or prolonged inflammatory phases. This enables autonomous, precise regulation of release timing and dosage for therapeutic components, transitioning from a passive response to active prediction and regulation. Ultimately, through convergence of materials science, microelectronics, bioinformatics, and clinical medicine, self-powered, bioabsorbable intelligent scar management systems capable of autonomously optimizing treatment strategies based on real-time diagnostic data will be realized. These systems will accelerate wound closure while proactively regulating repair quality and suppressing scar formation, representing a transformative advance in comprehensive management of recalcitrant wounds and advancing precision regenerative medicine.

Author contributions

All authors contributed to the article and approved the submitted version.

Conflicts of interest

The authors declare no conflicts of interest.

Data availability

No primary research results, software or code have been included and no new data were generated or analysed as part of this review.

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