Burns & Trauma, 2026, 14, tkag025
https://doi.org/10.1093/burnst/tkag025
Published: 18 March 2026
Review

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Advances in microneedle design for the delivery of drugs, proteins, and cells in the treatment of hypertrophic scars

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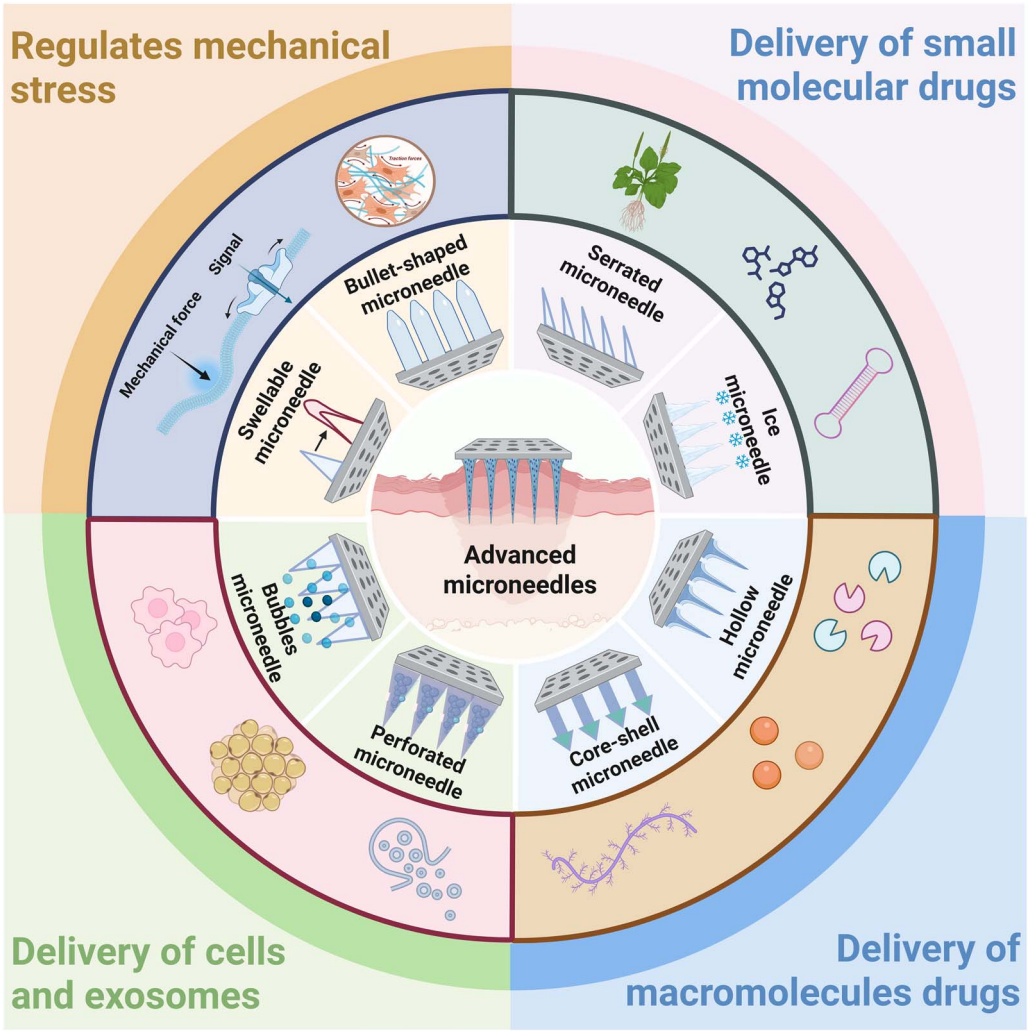
Abstract

Hypertrophic scars (HS) represent a significant clinical challenge due to their complex pathophysiology and resistance to conventional therapies, often resulting in persistent symptoms such as itching, pain, and impaired joint mobility that compromise patients' quality of life. Current treatment modalities, including compression therapy, pharmacological agents, radiation, silicone gel, and laser therapies, have faced limitations primarily due to inadequate drug penetration into the dense fibrotic scar tissue. In this context, microneedle-mediated controlled delivery systems have emerged as a promising pharmaceutical platform to enhance localized and sustained delivery of therapeutic agents, including small-molecule drugs, biologic proteins, small interfering RNA, and living cells, directly into HS. This article critically reviews the biological and formulation-related challenges associated with transdermal delivery in scar tissue and highlights recent innovations in microneedle design, material selection, and drug-loading techniques tailored for controlled release applications. Furthermore, it discusses the integration of proteins and cell-based therapies within microneedle platforms and their potential to modulate scar remodeling and inflammation. By addressing current limitations and exploring cutting-edge technologies, this review article aims to guide the development of effective microneedle-mediated strategies for pharmaceutical intervention in hypertrophic scar management.

Received: 12 November 2025. **Revised:** 11 March 2026. **Accepted:** 16 March 2026
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Graphical abstract



Keywords Microneedle, Drug delivery system, Hypertrophic scar, Wound healing

Background

A scar is defined as the visual, structural, and histopathological alteration of skin tissue following trauma, burns, surgical incisions, vaccinations, infections, or even insect bites. Scar formation represents a physiological, self-protective response by the human body [1] and can be classified into two types: hypertrophic scars (HS) and keloids (Figure 1) [2]. HS are characterized by excessive tissue proliferation confined to the boundaries of the original wound, without extending beyond it [3]. In contrast, keloids exhibit uncontrolled, persistent growth that extends beyond the original wound margins in all directions, often driven by sustained inflammation and genetic predisposition [4]. Such pathological distinction between hypertrophic scar and keloids suggests that HS, characterized by a localized fibrotic process, are particularly amenable to targeted local interventions, whereas keloids may require more systemic or combinatorial therapeutic approaches. Importantly, HS represent a highly prevalent clinical condition, with ~20 million new cases of HS occurring worldwide each year. Reported incidence rates ranging from 40% to >70%, and reaching up to 91% following burn injuries [5, 6]. HS can cause various undesirable symptoms, including itching, pain, and joint dysfunction, significantly reducing patients' quality of life and often leading to psychological distress [7].

In treating HS, common clinical interventions include compression therapy, which inhibits scar maturation by promoting the reversion of myofibroblast to normal fibroblasts during the early stage of scar formation [8–10]. Pharmacological approaches, such as steroids [11], botulinum toxin type A [12], antitumor agents [13], calcium channel blockers [14], and immunosuppressants [15], are also widely used to modulate cellular proliferation and apoptosis, thereby reducing fibrosis [16–18]. Radiation therapy is employed as an adjunct to induce scar atrophy by disrupting the dense capillary networks characteristic of early scars [19]. Additionally, laser therapies, including pulsed dye laser and Nd:YAG laser, selectively ablate scar vasculature, reducing erythema and pain through targeted vascular destruction, thereby inhibiting scar progression [20–23]. Despite therapeutic advances, hypertrophic scar management remains challenging. Pressure garments and elastic bandages often cause discomfort and poor compliance,

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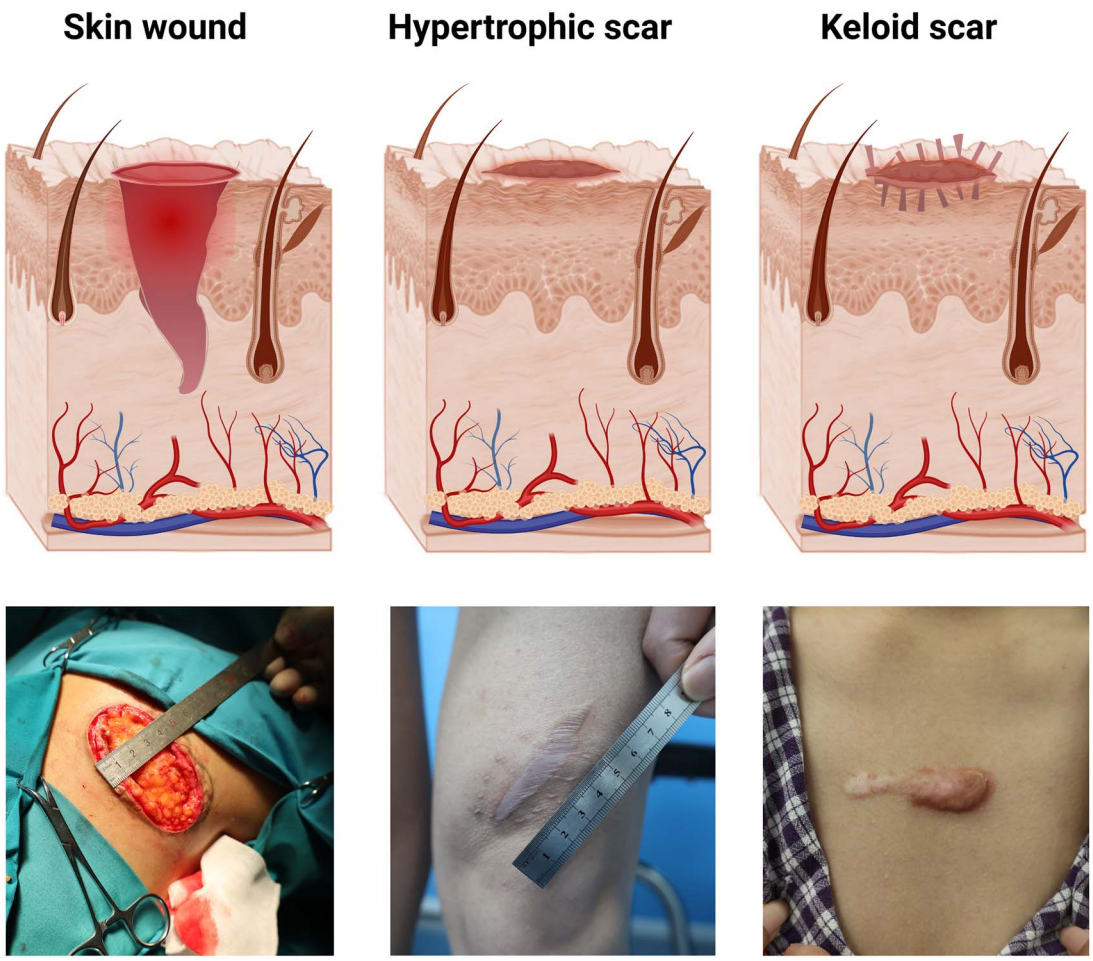


Figure 1 Schematic illustration and digital photos of skin wound, hypertrophic scars, and keloid scars (pictures were obtained from the Department of Plastic Surgery of Jiangsu Province Hospital of Chinese Medicine with the consent of the patients)

while repeated injections carry risks of uneven drug distribution and local adverse effects [24, 25]. Many of these limitations arise from a fundamental mismatch between existing treatment modalities and the unique pathological microenvironment of HS. These challenges highlight the need for novel, advanced delivery systems that are effective, targeted, intelligent, and well tolerated.

At the tissue level, the hypertrophic scar microenvironment itself poses substantial barriers to effective drug delivery, including (1) a dense, crosslinked extracellular matrix (ECM) rich in collagen and fibronectin that acts as a formidable physical barrier [26]; (2) aberrant mechanical stress signaling that perpetuates fibroblast activation and excessive ECM deposition [27]; and (3) a hypercellular and metabolically active tissue that may rapidly clear therapeutic agents [28]. Microneedle-based delivery systems are uniquely positioned to address these pathological features through rational structural and functional design. Specifically, microneedles with sufficient length, density, and mechanical strength can physically penetrate the stratum corneum and dense dermal ECM, enabling direct intralesional drug delivery. Moreover, tunable needle geometry and material composition allow modulation of local mechanical cues within the scar tissue and support sustained, localized drug release to counter rapid drug clearance. This targeted and minimally invasive approach offers distinct advantages over conventional topical formulations or intralesional injections for HS management, highlighting the unique suitability of microneedle platforms for addressing scar-specific pathophysiology.

Since 1976, microneedle patches have emerged as a promising transdermal delivery platform, creating microscale conduits in the skin that enable direct access to the dermis, thereby enhancing drug absorption and bypassing hepatic first-pass metabolism [24, 25]. Their customizable size, geometry, and material composition allow minimally invasive and largely painless administration [29] (Figure 2). Beyond serving as drug delivery vehicles, microneedle insertion itself can induce micro-injury, which has been shown to promote scar remodeling and tissue regeneration while reducing fibrosis [30]. Despite these advantages and their successful clinical translation in indications such as migraine, type 1 diabetes, and uveitis, no Food and Drug Administration (FDA) - approved microneedle-based products are currently available for hypertrophic scar therapy.

Review

Microneedle regulates mechanical stress in scar tissue

Mechanical stress plays a key role in scar formation. Fetal wounds typically heal without scarring due to minimal tension in fetal

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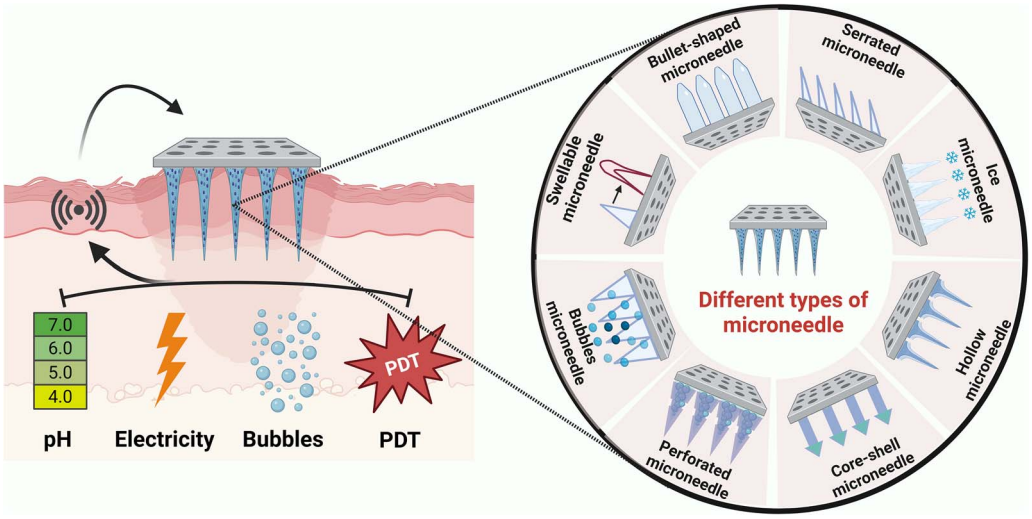


Figure 2 Advanced design of microneedle patches in treating hypertrophic scar. *PDT* photodynamic therapy

skin, while adult scars are aggravated by high skin tension and increased fibroblast activity [31]. Moreover, mechanical stress is not merely a physical driver but also a potent modulator of the local immune and inflammatory response in scar pathogenesis [32]. Excessive tension promotes the sustained infiltration and activation of immune cells, particularly driving macrophages toward a profibrotic M2 phenotype, and stimulates resident fibroblasts and keratinocytes to release inflammatory cytokines (e.g. Interleukin-1β (IL-1β), IL-6) and profibrotic mediators like transforming growth factor-beta 1 (TGF-β1). This creates a vicious cycle where inflammation enhances fibroblast activation and ECM deposition, which in turn increases tissue stiffness and further amplifies mechanical stress signaling. Additionally, various skin cells, including keratinocytes, fibroblasts, and immune cells, respond to mechanical stress by converting it into biochemical signals, activating molecular pathways that promote scar formation, including TGF-β1/Smad, MAPK, and ILK-PI3K/AKT, which regulate scar formation and cell proliferation [33–35].

Reducing tension at wound edges is known to minimize scarring. Microneedle interventions are reported to disrupt mechanical signal transmission between cells and the ECM, reducing collagen and fibronectin deposition while creating a low-stressed tissue environment [36]. A nontoxic microneedle patch using silk fibroin and polyvinyl alcohol has shown efficacy in inhibiting hypertrophic scar formation by blocking fibroblast communication with the ECM, downregulating TGF-β1, α-smooth muscle actin (α-SMA), collagen I, and fibronectin, thus reducing fibrosis [36]. Additionally, mechanical stress activates YAP, which promotes TGF-β/Smad signaling and fibrosis. Studies have shown that chemical inhibitors of YAP, such as verteporfin (VP), can mitigate these effects. When loaded into microneedles made of methacrylated silk fibroin protein, these inhibitors have been shown to effectively reduce mechanical tension by blocking YAP-mediated mechanical signal transduction, thereby preventing excessive scar formation [37, 38]. By targeting both the biochemical and mechanical pathways involved in scar formation, these innovative microneedles may have the potential to improve clinical outcomes in the general practice.

The length, array density, and mechanical hardness of microneedles are key design parameters that regulate mechanical stress within scar tissue and the associated mechanotransduction pathways [39]. Studies have shown that microneedles with a length of 500 μm exhibit limited therapeutic efficacy due to insufficient penetration into scar tissue, whereas 1500-μm microneedles, although capable of deep penetration, are prone to causing bleeding and inflammatory responses. In contrast, 1000-μm microneedles demonstrate the optimal therapeutic outcome in the rabbit ear hypertrophic scar model, as they effectively penetrate the dermal layer while minimizing tissue damage [36]. The array density of microneedles also influences the distribution of mechanical stress and modulation of the cellular microenvironment. High-density arrays (e.g. 15×15, $\sim$225 needles cm^{-2}) can significantly increase surface hydrophobicity, restrict cell migration and proliferation, and thereby more effectively disperse mechanical stress and inhibit fibroblast contraction. However, excessively high densities may lead to localized stress concentration at the needle tips, which can impede tissue remodeling. Therefore, an optimal balance between array density and stress uniformity must be achieved in practical microneedle design [36]. With respect to hardness, the mechanical strength of microneedles directly determines their puncture capability and efficiency of stress transmission. For single-polymer microneedles, mechanical strength can be enhanced through physical or chemical crosslinking, modulation of polymer crystallinity, and increasing polymer molecular weight. In addition, incorporating reinforcing agents or nano-/microparticles into microneedle matrices is an effective strategy for improving the mechanical strength of microneedles fabricated from brittle polymers [40].

Microneedle-based therapy for hypertrophic scar targets both the biochemical and biomechanical pathways involved in scar formation. While microneedling alone has demonstrated therapeutic benefits in hypertrophic scar management, conventional microneedles lack drug-delivery capability and therefore exert predominantly mechanical effects. This limitation prolonged and repeated treatments, which may compromise patient compliance. Microneedle delivery systems have shown efficacy in both immature and mature hypertrophic scar. In the early stage of scar formation, therapeutic strategies primarily aim to suppress aberrant cellular proliferation and inflammatory responses, whereas

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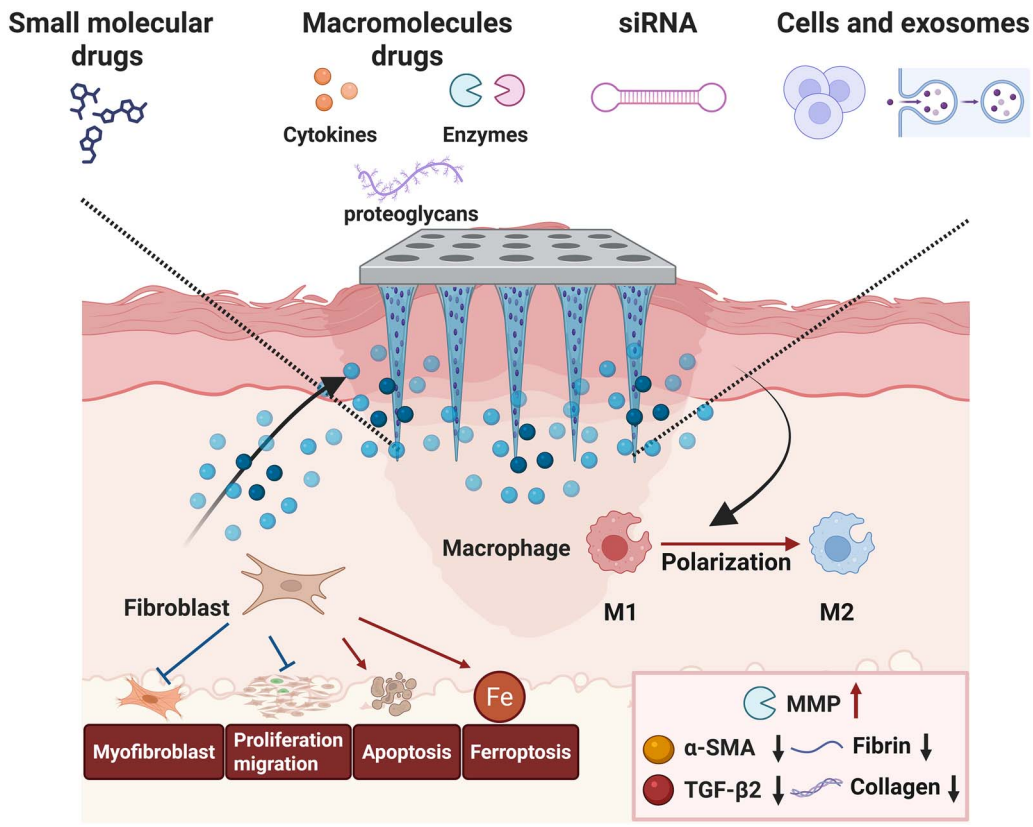


Figure 3 Microneedle-mediated controlled delivery of drugs, proteins and cells for treating HS. *siRNA* small interfering RNA, *MMP* matrix metalloproteinase, *α-SMA* α-smooth muscle actin, *TGF-β2* transforming growth factor-beta 2

treatment of mature scars focuses on collagen remodeling and ECM reorganization. Accordingly, microneedle systems should be rationally designed to match the pathological stage and underlying biological characteristics of HS. Although early clinical intervention is generally associated with improved outcomes, microneedle-based delivery systems, particularly when combined with adjunctive therapies, have also demonstrated potential in improving mature scars. Despite these advances, current studies lack systematic clinical investigations to define the optimal timing of microneedle-based interventions across different stages of HS development. Moreover, no microneedle delivery systems have yet been reported that can dynamically modulate drug release throughout the entire progression of scar formation, representing a critical gap and an important direction for future research.

Advanced microneedle delivery systems in the treatment of HS

Strategies for using microneedles to treat HS include directly applying microneedles to regulate mechanical stress in the scar tissue [36]. Research focuses more on using microneedles as delivery systems to deliver small molecular drugs, including various natural compounds, and chemical drugs [41–43]. Macromolecular drugs, such as cytokines [44], enzymes [45], and proteoglycans [46], and nucleic acid drugs represented by small interfering RNAs (siRNAs) [47], as well as cells and exosomes [48–51], can also be encapsulated and released via microneedle delivery system (Figure 3). To accommodate the unique physicochemical properties and mechanisms of action of therapeutic agents for HS treatment, researchers have tailored microneedle structural designs through the selection of specific materials, functional modifications, and optimization for scar applications. Microneedle design must be cargo specific. For small-molecule drugs, key considerations include improving solubility and precisely controlling release kinetics. For biologics such as proteins and nucleic acids, preserving stability and biological activity during fabrication and storage is paramount. For live cells and exosomes, maintaining post-delivery viability and biological functionality represents the primary challenge. Precise delivery to the dermis is the major advantage of microneedle, while it can also be used to increase skin permeability, improve bioavailability, trigger nonspecific immune responses, and modulate local mechanical stress with reduced pain and undesirable variability. These innovations aim to meet the therapeutic needs of HS across different clinical scenarios (Tables 1–4) [52-64].

Beyond cargo-specific considerations, the pathological evolution of HS further necessitates stage-specific microneedle design. The pathological features and therapeutic objectives of HS change dynamically over time. During the early inflammatory and proliferative phases, the primary goals are to suppress excessive inflammation and inhibit fibroblast hyperproliferation; thus, microneedles at this stage should enable rapid release of anti-inflammatory and antiproliferative agents [30, 65]. In contrast, mature scars are characterized by dense and highly remodeled ECM, where treatment strategies focus on degrading excessive collagen deposition and promoting its orderly reorganization [3].

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Table 1 Recent advancements of microneedle in delivering small molecular drugs

No	Active drugs	Materials	Advantages	Mechanical force	Release rate	Ref
1	TA	Dextran and polyethyleneimine	• Accurate local delivery • Better penetration	-	-	[52]
2	Losartan	Gelatin and starch	• Accurate local delivery • Sustained delivery • 3D printers enable customized design	0.30 N per needle	Drug release within 10 min	[53]
3	PA	HA and gelatin	• Accurate local delivery • Sustained delivery • Increase the mechanical strength of the microneedle	1.4 N per needle	Drug release within 10 min	[54]
4	OEO	Mucin, EC ethanol solution as backing layer	• Accurate local delivery • Backing layer is detachable	0.99 N per microneedle	The dissolution time of scar skin was 90 min, and that of normal skin was 80 min	[42]
5	Shikonin	HA	• Accurate local delivery	0.058 N/needle	–	[55]
6	Silver nanoclusters, trigonelline, and zeolitic imidazolate framework-8	GelMA	• Accurate local delivery • Sustained delivery • Intelligent pH responsivity	–	Cumulative drug release ≈73.2% within 24 h	[56]
7	Quercetin, HSF membrane, carbonate crosslinked cyclodextrin metal organic framework, and Bletilla striata polysaccharide	HA and PVP	• Accurate local delivery • Sustained delivery • Targeting fibroblasts	∼25 N	Cumulative drug releases ≈78.32 ± 0.80% within 24 h	[57]
8	Citric acid and $NaHCO_3$	PVP, PEG, and PLGA	• Accurate local delivery • CO_2 bubbles enhance drug penetration	0.68 N/needle	Drug release within 120 s	[58]
9	CuOx@MIL-101, chloroquine	Gelatin and starch	• Accurate local delivery • Combined photodynamic therapy enhances drug penetration • Increase the mechanical strength of the microneedle	Young's modulus >1 MPa	–	[59]
10	Verteporfin and heparin	PVA	• Accurate local delivery • Sustained delivery • Programmed regulation of inflammatory, proliferative, and remodeling phases • Combined with laser therapy	2.7 N per needle	Degradation during 24 h	[60]

TA triamcinolone acetonide, *PA* protocatechuic aldehyde, *HA* hyaluronic acid, *OEO* oregano essential, *EC* ethyl cellulose, *GelMA* gelatin methacrylate, *HSF* hypertrophic scar fibroblast, *PVP* poly (vinylpyrrolidone), *PEG* poly (ethylene glycol), *PLGA* poly (lactic-co-glycolic acid), *PVA* poly (vinyl alcohol)

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Table 2 Recent advancements of microneedle in delivering macromolecular drugs

No	Active macromolecules	Materials	Advantages	Mechanical force	Release rate	Ref
1	Interferon alpha 1b	CMC (8000 cp) as microneedle and CMC (36 cp) as backing layer	• Accurate local delivery • Sustained delivery • Backing layer is detachable	5.85 N	Cumulative release 88.7% within 30 min	[44]
2	HAase, 5-aminoevulinc acid, and metformin	CMC-Na and PVP K30	• Accurate local delivery • Better penetration	>14.4 N	Drug release within 20 min	[45]
3	rhPRG4	GelMA as microneedle and gelatin as backing layer	• Accurate local delivery • Sustained delivery • Regulate inflammatory response	-	>7 days	[46]

CMC carboxymethyl cellulose, *HAase* hyaluronidase, *PVP* poly (vinylpyrrolidone), *rhPRG4* recombinant human proteoglycan 4, *GelMA* gelatin methacrylate

Table 3 Recent advancements of microneedle in delivering siRNA

No	siRNA and therapeutic agents	Materials	Advantages	Mechanical force	Release rate	Ref
1	siRNA, gelatin, tyramine	HA	• Accurate local delivery • Sustained delivery	-	Release of 84.9 ± 13.8% at 60 min	[47]
2	SPARC siRNA	HA	• Low pain and pruritus • siRNA microneedle patches on 2-week-old surgical scars for 1–2 months can reduce scar tissue formation	–	–	[61]
3	siRNA	HA, $mSiO_2$, upconversion nanoparticles	• Enhance targeted delivery • Inhibit mitophagy, promote apoptosis, and modulate inflammation • Regulate macrophage polarization	0.08 N per needle	Release of 80% in 3 days	[62]

siRNA small interfering RNA, *HA* hyaluronic acid, *SPARC* secreted protein acidic and cysteine rich

Microneedle delivery of small molecular drugs

The small molecule drugs used for anti-scar formation therapy are summarized in Table 1 [52–60]. Their primary mechanisms include inhibiting fibroblast proliferation [30, 52, 53], preventing the transformation of fibroblasts into myofibroblasts [48], promoting fibroblast apoptosis [54, 56], modulating immune responses [60], and suppressing ECM production [66]. Commonly used drugs include glucocorticoids, such as the triamcinolone acetonide (TA) [41, 52], antitumor agents like 5-fluorouracil (5-FU) [13, 43] and bleomycin [13], angiotensin-converting enzyme inhibitors and angiotensin receptor blockers such as losartan [53], and natural active compounds and extracts from Traditional Chinese Medicine, including oregano essential oil [42] and shikonin [55]. However, when these drugs are directly applied to HS, low drug solubility that leads to poor formulation properties, short half-life, significant local irritation, and high toxicity and uncontrolled release within scar tissue are considered as the limitations.

Microneedle drug delivery systems are therefore further modified to increase the drug solubility of small molecules. TA is the most widely used drug for treating HS, exerting its anti-inflammatory effects by inhibiting fibroblast mitosis and suppressing macrophage polarization. However, due to its poor water solubility, TA is typically administered as a suspension in clinical settings, which is unsuitable for the formulation of microneedle fabrication. To address this, hydroxypropyl-β-cyclodextrin (HP-β-CD) encapsulation is utilized to improve the solubility of TA (Figure 4a). This approach was proved to significantly increase the drug-loading capacity of microneedles by ~4 times and their mechanical strength by ~2-fold. Animal studies have demonstrated that HA microneedles loaded with cyclodextrin-encapsulated TA significantly reduced the scar elevation index to normal levels, with decreased mRNA and protein expression of collagen I and TGF-β1 [41]. Similarly, nanotechnology-based approaches, such as nanoparticles in combination with microneedle delivery systems, are also proved to improve drug solubility by ~30 times, ensuring higher drug concentrations at the target site (Figure 4b) [57].

Microneedle delivery systems offer additional benefits by concentrating the drug within the scar tissue, minimizing its impact on surrounding healthy tissue. The antitumor drug 5-FU inhibits DNA synthesis in scar tissue cells, reducing collagen production, suppressing fibroblast proliferation, and limiting local vascular neogenesis [30]. However, due to rapid elimination by endogenous dihydropyrimidine dehydrogenase, 5-FU has a short

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Table 4 Recent advancements of microneedle in delivering cells and extracellular vesicles

No	Cells and active molecules	Materials	Advantages	Mechanical force	Release rate	Ref
1	MSCs	PLGA as shell and GelMA as core	• Accurate local delivery • Sustained delivery	>0.5 N	–	[63]
2	MSC-derived exosomes and mangiferin	GelMA as shell, PGLADMA as core	• Accurate local delivery • Sustained delivery • Regulate inflammatory response • Shell layer swells rapidly to enhance tissue-interlocking adhesion	0.25 N	48 h	[50]
3	HSF-derived exosomes and curcumin	Decellularized extracellular matrix from umbilical cord–derived mesenchymal stem cells	• Enhance targeted delivery • Inhibit mitophagy, promote apoptosis, and modulate inflammation • Regulate macrophage polarization	>0.1 N	–	[64]
4	ADSCC-CM and TA	Keratin and HA	• Accurate local delivery • Sustained delivery • Regulate inflammatory response	>0.1 N	>5 days	[51]
5	ADSC exosomes encapsulate miR-141-3p	HA and HP-β-CD as microneedle PVP K90 as backing layer	• Accurate local delivery • Sustained delivery • Increase the mechanical strength of the microneedle	257 N	Fast release within 20 min	[48]
6	CAR-TREM2-macrophages	PLGA, PEGDA, and $CaCO_3$	• Accurate local delivery • Sustained delivery • Regulate inflammatory response • Microporous structures enhance cell-loading efficiency	–	48 h	[49]

MSCs mesenchymal stem cells, *PLGA* poly (lactic-co-glycolic acid), *GelMA* gelatin methacrylate, *PGLADMA* poly (lactide-co-propylene glycol-co-lactide) dimethacrylate, *HSF* hypertrophic scar fibroblast, *ADSCC-CM* adipose-derived stem cell concentrated conditioned medium, *TA* triamcinolone acetonide, *HA* hyaluronic acid, *HP-β-CD* hydroxypropyl-β-cyclodextrin, *PVP* poly (vinylpyrrolidone), *PEGDA* poly (ethylene glycol) diacrylate

half-life, requiring higher doses and frequent administrations, which can lead to adverse effects such as depigmentation, skin atrophy, and capillary dilation. A two-layer microneedle array containing 5-FU and TA was therefore designed (Figure 4c) [43]. The needle body, made of chitosan and dextran, provides sustained release of 5-FU (50% of the drug remains in the tissue 24 h post-application compared to no detectable drug residue in the group treated with the drug solution), while the needle tail, composed of HA and HP-β-CD, facilitates rapid TA release. This dual-release design was proven to enhance efficacy, prolong drug retention at the lesion site, and improve patient safety. Additionally, such combinations utilizing both rapid and sustained release profiles have been employed with other drugs in treating HS. For example, dexamethasone combined with colchicine has shown greater effectiveness compared to either drug alone [67]. This strategy not only improves drug utilization but also reduces toxicity and side effects.

The low molecular weight of small-molecule drugs can cause rapid burst release from microneedles, making it difficult to achieve sustained therapeutic effects. Therefore, controlling the release rate remains as a significant challenge. Polymeric materials such as poly (lactic-co-glycolic acid) (PLGA) (Figure 5a) [50] and polycaprolactone (PCL) (Figure 5b) [68] are commonly used, aiming for sustained drug release. By adjusting the polymer ratios or crosslinking degrees, researchers are capable of enhancing the mechanical properties of microneedles while optimizing the drug release rate [60]. Moreover, polysaccharides, like HA, maltose, and chitosan, or low crosslinking polymers are found to be ideal for manufacturing rapid-dissolving microneedles. Small quantities of agents such as $NaHCO_3$, anhydrous citric acid (Figure 5c) [58], or magnesium particles (Figure 5d) [69] are also incorporated into the microneedle tips to generate gaseous microbubbles, promoting immediate drug release.

There are many types of small-molecule drugs and multiple therapeutic targets for treating HS. To enhance efficacy, various drugs can be further dual loaded to achieve synergistic effects across different targets. However, the complexity of dual-drug loading systems also presents a major challenge. Drug formulations have been integrated into different regions of the microneedles using a range of matrix materials, enabling controlled dual-drug release profiles. In addition, microneedles feature diverse structural designs, such as coated, encapsulated, and multilayered structures, which allow for controlled drug release, an essential feature in treating HS. One promising approach involves the “core–shell” microneedle patch, engineered based on the wound microenvironment (Figure 5e) [60].

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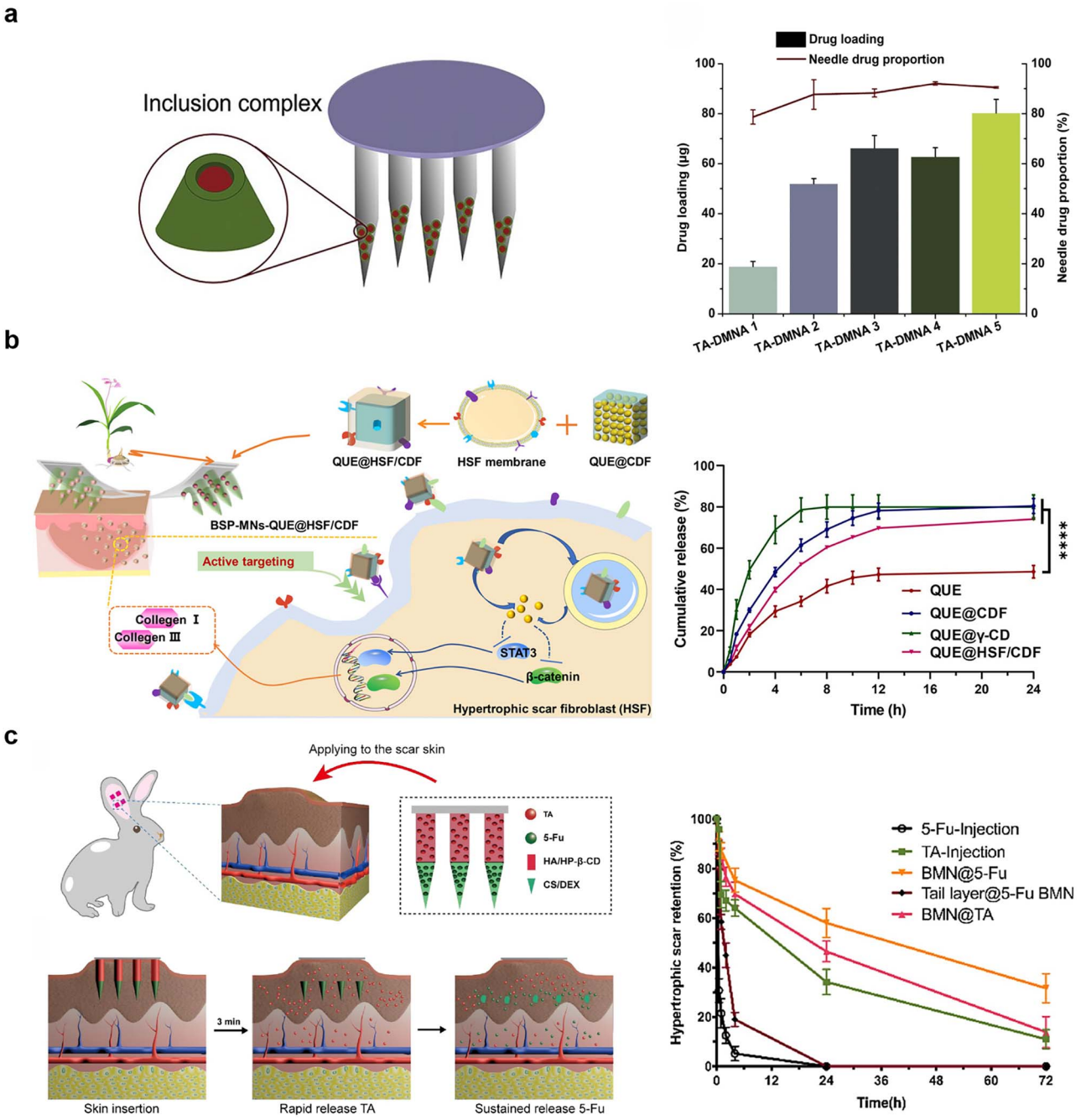


Figure 4 Microneedle enhances the solubility of small molecular drugs. (**a**) Combine HP-β-CD encapsulation with microneedle delivery systems to improve the solubility of TA [41]. Copyright 2019, Elsevier. (**b**) Combine nanoparticles with microneedle delivery systems to enhance the solubility of quercetin [57]. Copyright 2021, American Chemical Society. (**c**) A two-layer microneedle array offers a combination of rapid release and sustained release properties while prolonging drug retention at the lesion site. Reproduced from [43] under an open access license. *QUE* quercetin, *HSF* hypertrophic scar fibroblast, *CDF* cyclodextrin metal organic framework, *BSP Bletilla striata* polysaccharide, *TA* triamcinolone acetonide, *5-FU* 5-fluorouracil, *HA* hyaluronic acid, *HP-β-CD* hydroxypropyl-β-cyclodextrin, *BMN* bilayer dissolving microneedle, *CS* chitosan, *DEX* dextran

This design features a ROS-degradable polyvinyl alcohol shell loaded with VP, a fibroblast inhibitor, and a heparin-containing core. Heparin modulates the immune microenvironment by neutralizing inflammatory factors and shifting macrophages from an M1 (pro-inflammatory) phenotype to an M2 (anti-inflammatory) phenotype. This core–shell system has demonstrated potential in promoting macrophage polarization, facilitating the transition from inflammation to tissue proliferation. It also promotes angiogenesis and ECM deposition, ultimately leading to scar-free tissue regeneration [60]. Microneedles with drug coatings combine high penetration efficiency with rapid delivery, making them as dual therapeutic tools (Figure 5f) [70]. The programmable nature of these microneedle systems allows for multiphase drug release in a single application, maintaining a balance between the inflammatory, cell proliferation, and tissue remodeling phases of wound healing. This innovative strategy holds great potential for

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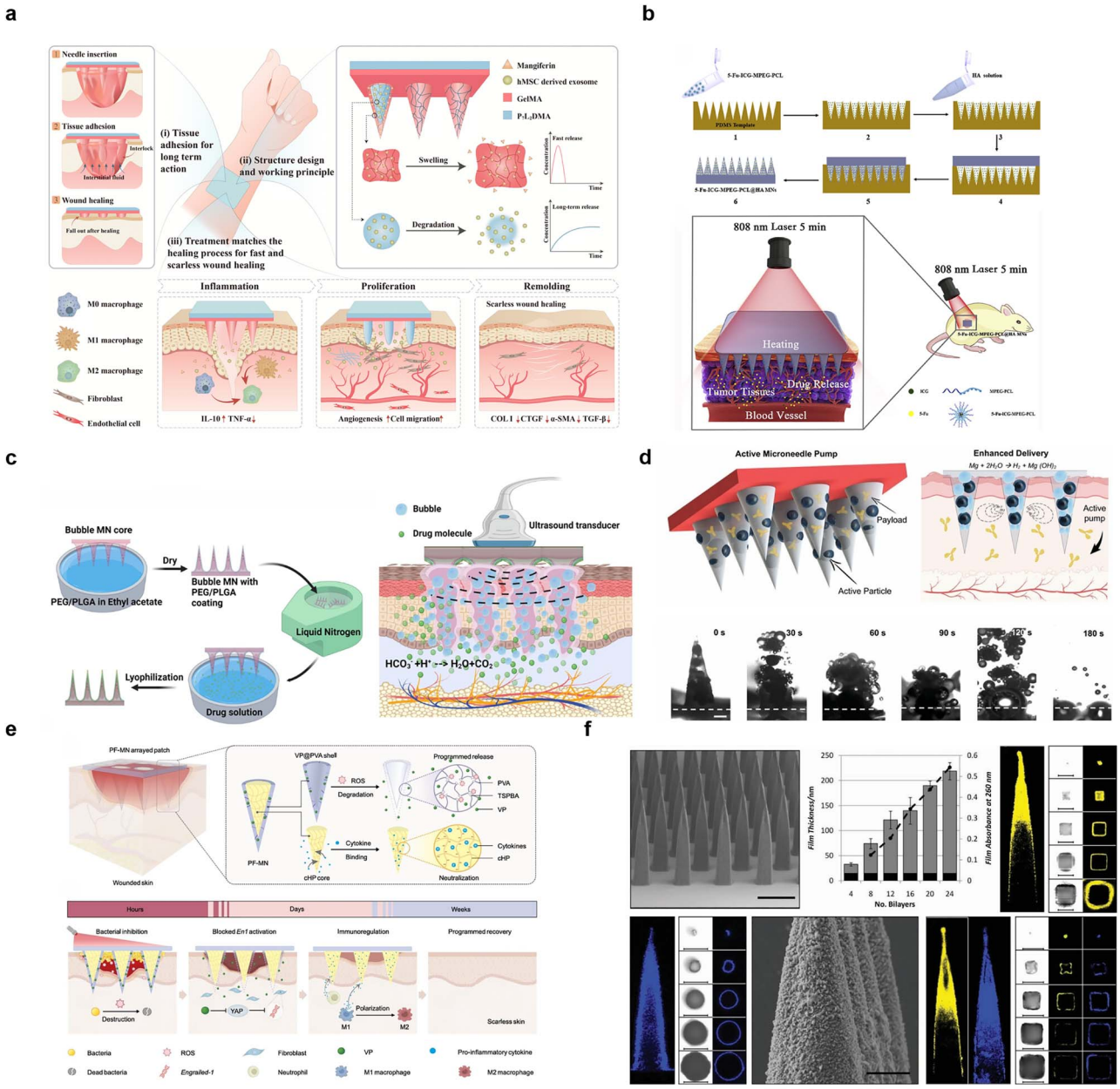


Figure 5 Microneedles enable small-molecule drugs to exhibit different release behaviors. Polymeric materials such as PLGA (**a**) [50] and polycaprolactone (**b**) [68] are commonly used aiming for sustained drug release in microneedles. Copyright 2014, Royal Society of Chemistry. Reproduced from [68] under an open access license. Small quantities of agents such as $NaHCO_3$, anhydrous citric acid (**c**) [58], or magnesium particles (**d**) [69] are incorporated into the microneedle tips to generate gaseous microbubbles, promoting immediate drug release. Copyright 2021, American Chemical Society. Copyright 2019, John Wiley and Sons. (**e**) A "core–shell" microneedle patch, a shell loaded with fibroblast inhibitor and a heparin-containing core, has demonstrated potential in promoting macrophage polarization, facilitating the transition from inflammation to tissue proliferation. Reproduced from [60] under an open access license. (**f**) Microneedles with drug coatings combine high penetration efficiency with rapid delivery [70]. Copyright 2010, John Wiley and Sons. *hMSC* human mesenchymal stromal cell, *GelMA* gelatin methacryloyl, *IL-10* interleukin-10, *TNF-α* tumor necrosis factor-alpha, *COL I* collagen I, *CTGF* connective tissue growth factor, *α-SMA* α-smooth muscle actin, *TGF-β* transforming growth factor-beta, *5-FU* 5-fluorouracil, *ICG* indocyanine green, *MPEG* monomethoxy-poly (ethylene glycol), *PCL* polycaprolactone, *HA* hyaluronic acid, *MN* microneedle, *PLGA* poly (lactic-co-glycolic acid), *PF* programmed functions, *VP* verteporfin, *ROS* reactive oxygen species, *Chp* crosslinked heparin, *PVA* poly (vinyl alcohol), *TSPBA* a ROS-responsive crosslinker

advancing the intelligent regulation of cutaneous wound-healing process, enabling multidrug co-loading and multitarget efficacy in scar management.

In addition to enhancing drug solubility and achieving controlled release, improving the local skin targeting of microneedle-based drug delivery systems represents an important strategy for HS treatment. One effective approach involves chemical modification of drug molecules or carriers to enhance targeting of specific cell types or subcellular organelles. For example, mannose-modified epigallocatechin gallate and metformin nanoparticles have been incorporated into separable core–shell microneedle patches fabricated from quaternized chitosan and

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ROS-degradable polymers. Mannose ligands bind to mannose receptors on the surface of macrophages, thereby promoting nanoparticle endocytosis, regulating mitochondrial function, and suppressing diabetic wound scar formation through downregulation of the IL-17/PI3K/Akt signaling pathway. This design enables microneedle systems to integrate multiple functions, including skin penetration, controlled drug release, cellular targeting, and immunomodulation, thereby advancing microneedles into multifunctional and integrated material platforms [71]. Moreover, local bioactive enzyme activity within the skin plays a crucial role in modulating drug efficacy. Accordingly, the development of enzyme-targeted microneedle drug delivery systems provides a promising new direction for HS therapy. For instance, prednisone-loaded silk fibroin microneedles have been shown to upregulate the expression of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) in local tissues, an enzyme responsible for converting inactive glucocorticoids into their active forms. These microneedles enable sustained prednisone release for up to 7 days. Following release at the target site, prednisone is locally activated *in situ*, thereby accelerating scar tissue remodeling, reducing scar area, and inhibiting fibrosis. This enzyme-targeted delivery strategy not only optimizes local glucocorticoid metabolism and enhances tissue penetration but also markedly reduces the systemic side effects associated with active glucocorticoids [72].

As the physiological barriers of the hard-textured stratum corneum and the dense ECM of scar tissue significantly hinder transdermal penetration and intracellular drug delivery [45], exogenous adjuvant therapies, such as light-sensitive [59] or electrical stimulation [73] approaches, are often combined with microneedle drug delivery systems [74]. Photodynamic therapy (PDT) has demonstrated clinical efficacy in reducing HS and improving scar pliability. When combined with microneedles, this approach provides great advantages of being minimally invasive and highly controllable. Researchers also designed microneedle arrays that incorporate a photosensitizer, enabling the microneedles to penetrate both porcine skin and rabbit ear scar tissue [59]. The microneedle patches possess sufficient mechanical strength to deliver the photosensitizer deep into the scar tissue and enhance the sustained release of the active drug, achieving deeper anti-scar effects through PDT [59].

Taken together, while small molecular drugs target key pathways in hypertrophic scar formation, their clinical translation is hampered by inherent physicochemical limitations such as poor solubility and poor targeting. Microneedle delivery systems emerge as a potent strategy to overcome these barriers. They enhance drug solubility and loading capacity through cyclodextrin encapsulation or nanotechnology, enable controlled release and co-delivery of two drugs via sophisticated material designs (e.g. core–shell structures), and facilitate combination therapies for synergistic multitarget effects and enhance the targeting of local cells, organelles, and bioactive enzymes. While microneedle systems match the efficacy of some conventional treatments and improve drug delivery efficiency, their small size limits drug loading, requiring more potent drugs and advanced formulations to increase capacity in future development. On the other hand, high drug loading may lead to insufficient hardness of microneedles, such as the risk of fracture, and a balance between drug loading and mechanical strength is also needed.

Microneedle delivery of macromolecular drugs

Unlike small-molecule drugs, macromolecular drugs, especially protein, offer target specificity, high efficacy, and minimal side effects [75]. However, their larger molecular weight, hydrophilicity, and susceptibility to denaturation and inactivation result in slower transdermal diffusion in hypertrophic scar tissues [75, 76]. Additionally, they are more sensitive to environmental conditions during preparation, storage, transportation, and application [77]. Current research on protein-based drugs for hypertrophic scar therapy includes cytokines [44], enzymes [45], and proteoglycans [46]. However, there has been limited investigations of microneedle delivery systems for these protein-based therapies despite their potential as a promising treatment strategy. Soluble microneedles may be suitable for administering protein-based drugs. Typically composed of dissolvable materials that incorporate the drug into the microneedle body, these devices allow for efficient drug delivery into the skin through the dissolution of the microneedle matrix. Importantly, soluble microneedles leave no harmful residues after penetration into skin. Furthermore, the microneedle preparation is mild, avoiding high temperatures, extreme pH, or organic solvents, which can maintain the stability of protein-based drugs.

Interferons are a class of cytokines known for their antiviral and antiproliferative effects [78]. They induce apoptosis, inhibit fibroblast proliferation, enhance collagenase activity, and downregulate collagen production [78, 79]. The application of interferon-loaded, detachable bilayer soluble carboxymethylcellulose polymer microneedle patches has demonstrated significant efficacy in treating HS (Figure 6a). In these patches, the second layer dissolves rapidly upon insertion, allowing the microneedle tip, which contains interferon, to remain in the skin and provide sustained release of the drug. This approach effectively inhibits fibroblast proliferation and reduces collagen deposition, leading to notable reductions in scar color and thickness [44]. Additionally, the relative expression of collagen I, collagen III, TGF-β, and α-SMA was significantly downregulated in the scar tissue.

Hyaluronic acid (HA) is a key component of the ECM, where it is tightly bound to collagen fibers and acts as a barrier to the diffusion or penetration of anti-scarring drugs. To address this challenge, hyaluronidase has been used to overcome the dual barrier posed by the stratum corneum and the ECM [80]. Hyaluronidase is an enzyme that specifically degrades HA. It breaks down the HA content in the tissue, leading to a softer and more permeable matrix, which facilitates the diffusion of injected drugs and exudates from the localized lesion area [81]. The application of hyaluronidase has been shown to enhance the diffusion of FDA-approved 5-aminolevulinic acid (ALA), offering an alternative strategy to inhibit ECM barriers [82]. A novel delivery system was developed by combining ALA with HAase-loaded microneedles, forming a soluble microneedle co-delivery system (Figure 6b). This system leverages the permeation-enhancing effect of hyaluronidase, acting as a “spear” to promote ALA penetration, induce fibroblast apoptosis, activate relevant signaling pathways, and ultimately enhance the anti-scarring effect [45].

Recombinant human proteoglycan 4 (rhPRG4) can modulate macrophage polarization and prevent fibrosis and scar formation during wound healing. However, its large molecular weight limits skin penetration and diffusion. Biodegradable gelatin

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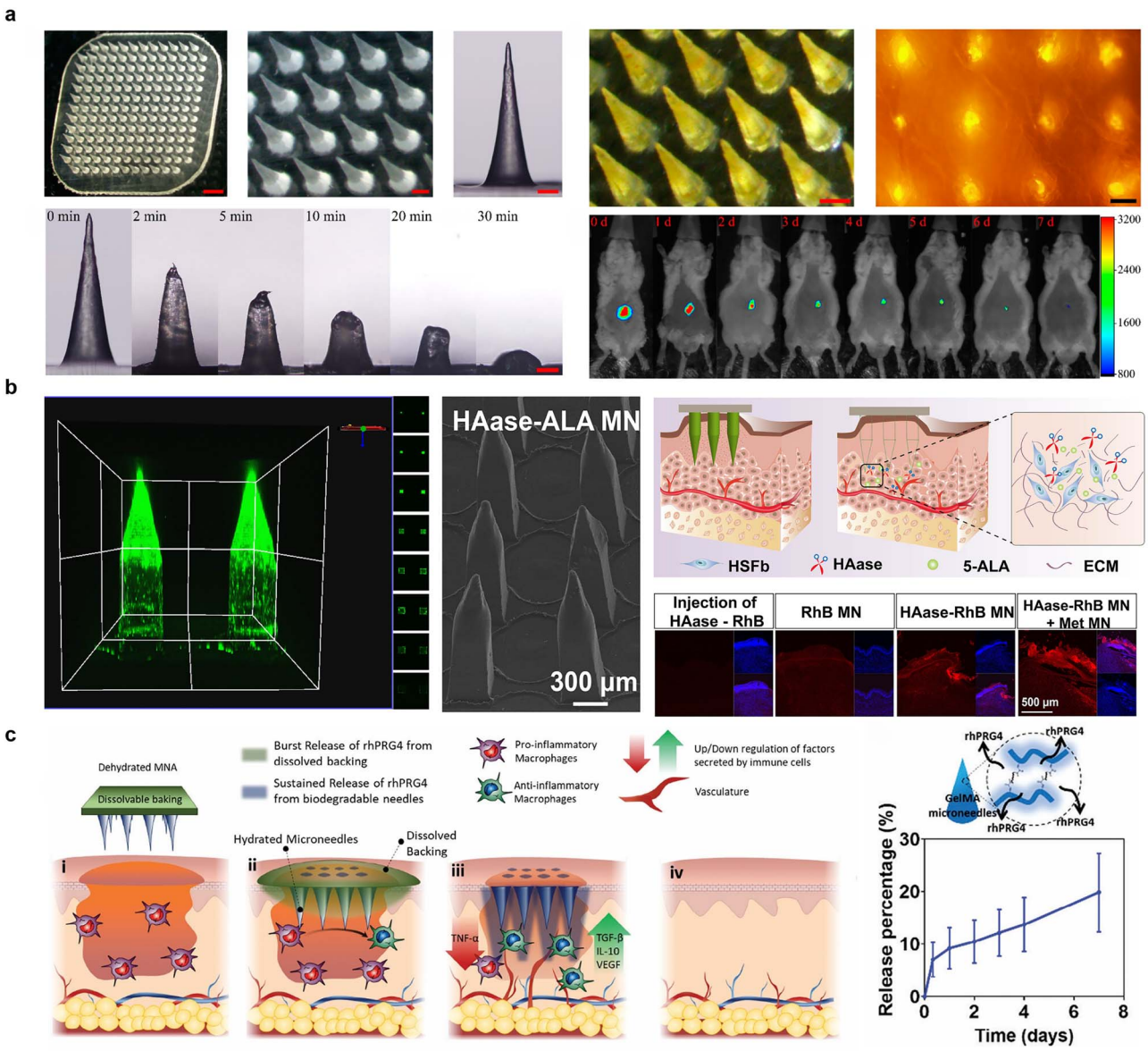


Figure 6 Microneedle-mediated delivery of macromolecular therapeutics for hypertrophic scar treatment. (**a**) The application of interferon-loaded, detachable bilayer soluble carboxymethylcellulose polymer microneedle patches has demonstrated significant efficacy in treating HS. Reproduced from [44] under an open access license. (**b**) A novel delivery system was developed by combining ALA with HAase-loaded microneedles, forming a soluble microneedle co-delivery system [45]. Copyright 2022, Elsevier. (**c**) Biodegradable GelMA hydrogel microneedles have been developed to deliver rhPRG4 directly into the lesion [46]. Copyright 2024, John Wiley and Sons. *HAase* hyaluronidase, *ALA* aminolevulinic acid, *MN* microneedle, *HSFb* hypertrophic scar fibroblast, *ECM* extracellular matrix, *RhB* rhodamine B, *TNF-α* tumor necrosis factor-alpha, *TGF-β* transforming growth factor-beta, *IL-10* interleukin-10, *VEGF* vascular endothelial growth factor, *GelMA* gelatin methacryloyl, *rhPRG4* recombinant human proteoglycan 4

methacryloyl (GelMA) hydrogel microneedles have been developed to deliver rhPRG4 directly into the lesion (Figure 6c). In this microneedle system, rhPRG4 is loaded into a dissolvable backing layer and slowly degradable GelMA microneedles. Upon insertion into the tissue, the backing layer dissolves, releasing rhPRG4 into the wound, while the GelMA microneedles gradually release the drug, maintaining its local concentration and bioavailability [46].

In contrast to small molecules, macromolecular drugs offer high target specificity and efficacy but face challenges in transdermal delivery due to their large size, hydrophilicity, and instability. Soluble microneedles provide a promising strategy for delivering these biologics. These MNs are typically fabricated from biocompatible and dissolvable polymers such as GelMA, enabling mild processing conditions (avoiding high temperature, organic solvents, or extreme pH), thus preserving the stability and bioactivity of macromolecules and enabling efficient intradermal release. Examples include interferon-loaded microneedles for sustained antiproliferative and antifibrotic effects, hyaluronidase-based systems for enhanced penetration through ECM degradation, and proteoglycan-loaded biodegradable microneedles for prolonged bioavailability and immunomodulation. Although soluble microneedles show great promise for delivering macromolecular drugs, several challenges remain. These include maintaining the mechanical strength of the needles after drying to prevent bending or breaking during penetration of scar tissue. Additionally, for microneedles delivering bioactive macromolecular drugs,

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especially protein-based drugs, it is important to ensure that the concentration of the matrix material does not compromise the protein's activity and to avoid vibrations during the preparation process that could lead to protein denaturation.

Microneedle delivery of nucleic-acid drug (siRNA)

In microneedle-mediated treatment of HS, nucleic acid therapeutics such as siRNA have attracted considerable attention due to their ability to target pathogenic genes and precisely regulate gene expression. As short double-stranded RNA molecules, siRNAs specifically silence target mRNA through the RNA interference mechanism, thereby intervening in disease progression at the genetic level. Previous studies have demonstrated that siRNA-mediated silencing of key profibrotic factors, such as connective tissue growth factor [83] or transforming growth factor-β [62], can effectively inhibit fibrotic processes. However, siRNA is inherently susceptible to enzymatic degradation, and its *in vivo* delivery efficiency remains low. Moreover, conventional delivery carriers, such as exosomes [84], are often associated with complex preparation procedures and limited stability, which together severely restrict the clinical translation of siRNA-based therapies.

Microneedle technology provides an effective and minimally invasive platform for the transdermal delivery of siRNA. By penetrating the stratum corneum, microneedles enable direct deposition of siRNA into the dermis, where it can be internalized by target cells to exert gene-silencing effects. A randomized controlled study conducted at a dermatology center demonstrated that postoperative wounds treated with siRNA-loaded microneedle patches exhibited a significant reduction in scar volume after 60 days, confirming both the efficacy and safety of this approach for inhibiting scar formation [61]. To improve siRNA stability during delivery, a range of protective strategies have been developed. For instance, siRNA can be assembled with gelatin and tyramine to form nanocomposites and subsequently incorporated into sodium hyaluronate–based microneedles, thereby enhancing resistance to enzymatic degradation and prolonging therapeutic activity [47]. Animal studies have shown that this system delays wound contraction and reduces collagen deposition, ultimately suppressing scar formation. Similarly, encapsulating siRNA within mesoporous silica nanoparticles prior to microneedle loading not only protects siRNA from degradation but also promotes tissue diffusion and intracellular uptake, further enhancing gene-silencing efficiency and offering a promising strategy for localized siRNA therapy [62].

Despite these advances, siRNA-loaded microneedle systems still face few challenges, including limited stability at room temperature, potential immunogenicity, and difficulties in large-scale manufacturing. Future strategies may involve the use of immunomodulatory polymers, such as poly[di (carboxyphenoxy) phosphazene], as microneedle matrices [85], or the development of frozen microneedle platforms to better preserve siRNA bioactivity. In parallel, further improvements in siRNA stability may be achieved through integration with nanocomposites, mesoporous coatings, and related technologies. Nevertheless, the source availability and high synthesis cost of siRNA remain major bottlenecks for its clinical translation and large-scale application.

Microneedle delivery of cells and exosomes

Therapeutic cells, such as stem cells and macrophages, along with their derived extracellular vesicles (such as exosomes), can be directly delivered to pathological sites using microneedle-based systems [49, 63]. Compared to the commonly used intravenous infusion method, microneedle transdermal delivery enhances tissue targeting and reduces the risk of off-target effects in systemic circulation [86] and also prolongs local retention time and expands the potential applications of cell therapy in tissue regeneration and repair [64, 87]. An overview of microneedle-based delivery designs for various cell types in the treatment of HS is provided in Figure 7 and Table 4.

Stem cells are renowned for their immunomodulatory, anti-inflammatory, and antifibrotic properties, showing promise in preventing and treating excessive scar formation [88]. Mesenchymal stem cells (MSCs), adipose-derived stem cells (ADSCs), and human amniotic epithelial cells are widely studied [89], and induced pluripotent stem cells [90] are currently at the forefront of scar treatment research [91–93]. Moreover, stem cell–derived exosomes and nano-sized vesicles (30–200 nm) were proved to inhibit collagen expression and reduce myofibroblast proliferation, thereby facilitating ECM remodeling [94]. Beyond their role in intercellular communication, exosomes contribute to ameliorating fibrotic tissue conditions and promoting scar-free healing. Their lipid bilayer structure enables efficient drug loading, while surface-specific proteins and glycans inherited from parent cells confer a natural "homing effect," allowing targeted uptake by recipient cells (Figure 7c) [64]. Microneedle systems provide an innovative strategy for enhancing the cutaneous delivery of stem cells and their exosomes, significantly improving therapeutic outcomes in hypertrophic scar treatment. Studies indicate that MSCs and MSC-derived exosomes alleviate scar formation by modulating macrophage activity, suppressing M1 polarization, and regulating ECM deposition [95]. A study employing GelMA combined with MSCs demonstrated that GelMA + MSC microneedles encapsulated in a PLGA shell effectively delivered cells to the wound bed (Figure 7a). The MSCs retained over 24% viability for up to 90 h. This microneedle patch exhibited superior therapeutic efficacy compared to direct MSC injections or microneedles without MSCs. Notably, it significantly reduced fibrotic tissue thickness on the wound surface, indicating the potential of microneedle delivery of live cells for minimizing proliferative scarring [63].

ADSCs have demonstrated significant potential in mitigating fibrosis through promoting angiogenesis, stimulating mitosis in resident tissue cells, remodeling the ECM [96], and modulating inflammatory cell activity [97]. Their therapeutic potential in the treatment of hypertrophic scarring is well documented [98]. In 2024, a study reported that ADSC-concentrated conditioned medium (ADSCC-CM) can promote keratin hydrogel crosslinking, which facilitates the formation of a novel keratin microneedle patch incorporating TA as a dual-drug delivery system (Figure 7b) [51]. After 4 weeks of administration in a rabbit ear scar model, the treatment effectively inhibited myofibroblast overactivation by reducing inflammation and reshaping the ECM, thereby minimizing scar formation. Beyond the regenerative properties of ADSCs, exosomes derived from ADSCs have been shown to inhibit scar proliferation by preventing fibroblast-to-myofibroblast differentiation and upregulating MMP-3 expression in dermal fibroblasts, which aids in collagen remodeling [99].

Recent advancements in cell delivery via microneedle technology have focused on genetically engineering cells to enhance their therapeutic efficacy. One promising development involves the

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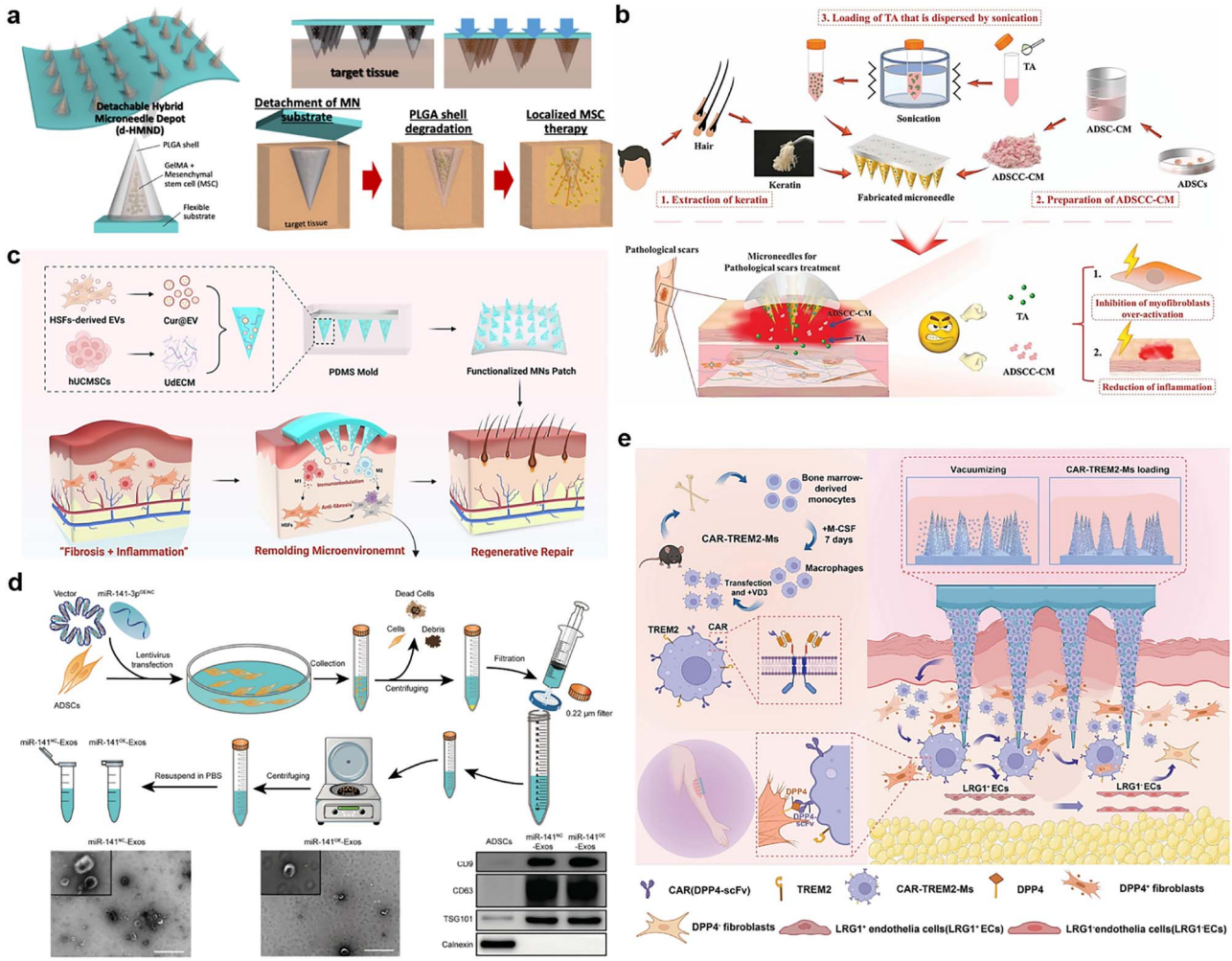


Figure 7 Application of microneedle delivery of cells and exosomes. (**a**) Graphical abstract of an assembled d-HMND consisting of an array of MNs with PLGA shells, filled with a GelMA–MSC mixture, and fixed to a flexible substrate [63]. Copyright 2020, John Wiley and Sons. (**b**) Schematic illustration of the fabrication and administration of TA@AC-MN for pathological scar (PS) treatment. TA@AC-MN consists of extracting human hair–derived keratin and ADSCC-CM, improving the dispersion stability of the TA solution; the mechanism of TA@AC-MN in PS treatment is through the synergistic effect of TA and ADSCC-CM on myofibroblast phenotype and tissue inflammation inhibition [51]. Copyright 2024, John Wiley and Sons. (**c**) Scheme of the functionalized MN patch that was loaded with targeted cur@EV and UdECM for the treatment of HS by inducing apoptosis in HSFs, promoting M2 polarization in macrophages and restoring microenvironment homeostasis. Reproduced from [64] under an open access license. (**d**) The preparation and identification of engineered exosomes, TEM representative images (scale bar, 1 μm), and protein expression of CD9, CD63, TSG101, and Calnexin in ADSCs, miR-141-3p NC-exos, and miR-141-3p OE-exos [48]. Copyright 2023, John Wiley and Sons. (**e**) Schematic of CAR-TREM2-M delivery by mMNs to target fibroblasts and regulate ECs' fibrotic phenotype to promote wound regeneration without scarring [49]. Copyright 2024, John Wiley and Sons. *PLGA* poly (lactic-co-glycolic) acid, *GelMA* gelatin methacryloyl, *MN* microneedle, *TA* triamcinolone acetonide, *ADSCs* adipose-derived stem cells, *ADSC-CM* adipose-derived stem cell conditioned medium; *ADSCC-CM* adipose-derived stem cell concentrated conditioned medium, *HSFs* hyperplastic scar fibroblasts, *EVs* extracellular vesicles, *cur* curcumin, *hUCMSCs* human umbilical cord–derived mesenchymal stem cells, *UdECM* UCMSC-derived decellularized extracellular matrix, *PDMS* polydimethylsiloxane, *CAR-TREM2-Ms* CAR-TREM2-macrophages, *LRG* leucine-rich-alpha-2-glycoprotein, *DPP4* dipeptidyl peptidase 4

incorporation of miRNA-modified exosomes derived from ADSCs in HA-based microneedles (Figure 7d). This approach enables targeted delivery of therapeutic agents to scar tissue. The application of HA microneedles demonstrated significantly enhanced efficacy in suppressing fibroblast proliferation, migration, and myofibroblast differentiation *in vitro*, contributing to improved scar tissue architecture and appearance [48]. In another recent study, genetic editing techniques were employed to enhance the targeting capability and induction efficiency of cell delivery (Figure 7e). Specifically, macrophages were engineered to express a chimeric antigen receptor (CAR) targeting dipeptidyl peptidase-4 (DPP4), inducing a TREM2$^+$ macrophage phenotype (CAR-TREM2-M). These cells were effectively loaded and delivered using hydrogel-based porous microneedles. The microneedle system modulated fibrosis-related gene expression by suppressing leucine-rich α-2-glycoprotein 1, a key profibrotic gene. Furthermore, it significantly ameliorated the scar immune microenvironment through phagocytosis of DPP4$^+$ fibroblasts and inhibition of TGF-β secretion, offering a novel strategic approach for scar treatment [49]. In the future, advanced bioengineering strategies are expected to enable the development of cell-specific microneedle delivery systems. For instance, microneedles could

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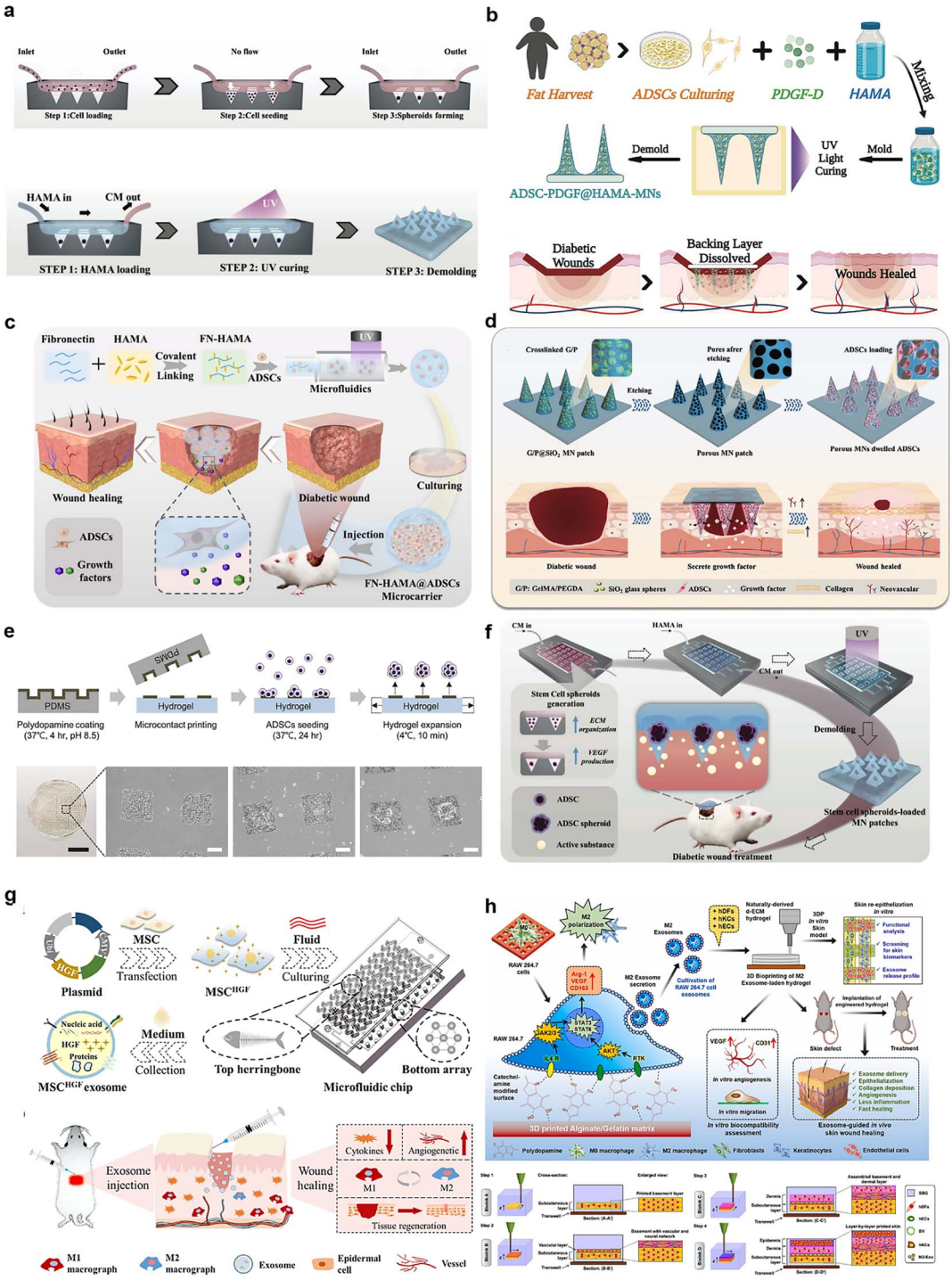


Figure 8 Design and strategies of microneedle delivery of cells and extracellular vesicles. (**a**) Schematic of MN@SP fabrication processes, including HAMA loading, UV curing, and demolding [101]. Copyright 2023, John Wiley and Sons. (**b**) Schematic illustrations of the MN system loaded with ADSCs and PDGF-D [104]. Copyright 2022, John Wiley and Sons. (**c**) Schematic of the fabrication of fibronectin (FN)–HAMA microcarriers with ADSC encapsulation. Reproduced from [105] under an open access license. (**d**) Schematic diagram of the preparation of porous MNs loaded with ADSCs bio-inspired by stem cell niches [106]. Copyright 2024, John Wiley and Sons. (**e**) Illustration of the harvesting of ADSC spheroids from hydrogels [107]. Copyright 2022, Elsevier. (**f**) Fabrication of the microfluidic templated ADSC spheroid microneedles [101]. Copyright 2023, John Wiley and Sons. (**g**) Genetically engineered stromal cell exosomes from high-throughput herringbone microfluidics [112]. Copyright 2025, American chemical. (**h**) 3D bioprinting of engineered exosomes from M2-polarized macrophages. Reproduced from [113] under an open access license. *HAMA* hyaluronic acid methacryloyl, *ADSCs* adipose-derived stem cells, *PDGF-D* platelet-derived growth factor D, *FN* fibronectin, *GelMA* gelatin methacryloyl, *PEGDA* poly (ethylene glycol) diacrylate, *MN* microneedle, *PDMS* poly (dimethylsiloxane), *ECM* extracellular matrix, *VEGF* vascular endothelial growth factor, *MSC* mesenchymal stromal cells, *HGF* hepatocyte growth factor, *Arg-1* arginase 1, *hDFs* human dermal fibroblasts, *hKCs* human keratinocytes, *hECs* human endothelial cells

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be integrated with highly efficient reprogramming protocols using small-molecule cocktails to induce transdifferentiation of fibroblasts into functional cell types such as adipocytes or hair follicle cells [100], thereby promoting functional tissue regeneration in scar areas rather than merely suppressing fibrosis.

In the preparation of microneedles, centrifugation or vacuum loading is commonly used to load the cargo, often combined with heating and drying to enhance needle mechanical stiffness. However, these processes can compromise the viability of cells and exosomes. To improve cell survival rates, several advanced strategies have been proposed (Figure 8). First, photo-crosslinked hydrogels such as GelMA and hyaluronic acid methacryloyl (HAMA) are polymerized via UV irradiation (Figure 8a) that can avoid desiccation-induced damage [101]. This method is rapid, mild, and minimally impacts cellular viability [102, 103]. Second, incorporating nutrients such as growth factors (Figure 8b) [104] or ECM components [63] to provide cell-adhesive motifs enhances post-loading cell survival. Inspired by the stem cell niche (Figure 8c) [105], researchers have co-loaded ADSCs with biomimetic ECM microenvironments into microneedles to enhance their bioactivity and tissue regenerative capacity (Figure 8d) [106]. Third, using three-dimensional (3D) cell spheroids instead of single cells improves environmental resistance and cell communication (Figure 8e), better replicating *in vivo* tissue characteristics [107]. However, conventional methods such as suspension culture or low-attachment plates often yield spheroids with heterogeneous sizes [108]. Oversized aggregates suffer from central hypoxia, impairing their viability and functionality [109]. Microfluidic technology (Figure 8f) enables precise fluid control to produce 3D cell spheroids with uniform size and controlled cellular distribution [101], allowing high-throughput and automated fabrication via multichannel architectures [110]. Beyond serving as a cell culture platform, microfluidic chips can be functionalized to act as versatile "micro-reactors" (Figure 8g), achieving highly integrated systems for cell manipulation, such as enhanced tissue adhesion [111, 112] and targeting capability Furthermore, 3D bioprinting technology facilitates the co-culture of fibroblasts, keratinocytes, stem cells, and endothelial cells (Figure 8h), holding great potential for future precision therapy in HS [113].

Although microneedle delivery systems offer a promising approach to address challenges in cell viability and functional maintenance in cell-based therapies, several limitations remain. Material innovations (dissolving and hydrogel-based microneedles) and structural designs (hollow, porous, and ice microneedles) have been developed to enhance delivery efficiency into deeper skin layers (Figure 2) [114]. Dissolving microneedles typically incorporate cells into water-soluble polymers (e.g. gelatin, sodium alginate, HA) followed by solidification, making them suitable for rapid cell release applications such as vaccination or acute treatments [115]. In contrast, hydrogel microneedles allow precise control over pore size, mechanical strength, and degradation kinetics through tunable crosslinking, ideal for sustained release scenarios requiring long-term cell survival [116]. Hollow microneedles facilitate the delivery of large cell volumes and protect cells before administration, yet their application is constrained by limited biocompatibility, mechanical robustness, and structural complexity [117]. Porous microneedles provide higher specific surface area than solid microneedles, significantly improving cell-loading efficiency, though they often suffer from reduced mechanical strength and complicated fabrication processes [49]. Ice microneedles represent a novel strategy for enhancing cell preservation and immune-compatibility [114, 118], enabling precise control over delivered cell numbers [119]. Despite these advantages, issues such as susceptibility to melting, demanding preparation conditions, and the requirement for ultra-cold chain logistics remain unresolved. Conventional microneedle manufacturing primarily relies on molding techniques, which restrict design flexibility. 3D bioprinting technology enables the fabrication of patient-specific microneedle patches tailored to scar morphology (Figure 8h) [113, 120], overcoming drug distribution heterogeneity in irregular scars. This approach allows integration of multiple cargo types (drugs, matrix materials, and cells) within a single array, offering precise spatial control over composition and enhancing differentiation efficiency. However, the technology demands stringent requirements regarding bioink rheology, biocompatibility, and printing precision. Additionally, personalized fabrication introduces elevated costs and developmental challenges, currently limiting its application to laboratory-scale research.

In summary, the optimal strategy for microneedle-based treatment of HS via cell delivery involves an integrated platform approach: employing photo-crosslinked hydrogel microneedles that mimic a favorable cellular microenvironment as the delivery vehicle, loaded with multicellular spheroids capable of multitarget therapy. This may be further combined with genetic editing techniques for precise regulation of cell behavior and tissue regeneration processes, alongside advanced manufacturing technologies such as microfluidics to achieve standardized, high-throughput, and personalized production.

Conclusions

This review highlights the potential of microneedle patches as a novel therapeutic and drug delivery strategy for HS, while also addressing the limitations of current clinical treatments. Advances in microneedle design now enable the incorporation of diverse agents, including small molecules, biologics, cells, and exosomes, broadening their applicability for scar management. However, several challenges remain, including the drug loading to mechanical strength trade-off, where high drug concentrations can compromise needle integrity and necessitate innovative composites or nanostructure. Additionally, the preservation of delivered substances as well as the stability of proteins, nucleic acids, and particularly the viability of cells during fabrication, storage, and post-administration remains a critical hurdle. Moreover, personalized manufacturing requires adapting microneedle geometry and drug combinations to highly variable individual scar morphology and stage, posing technological and economic challenges. Finally, there is a lack of long-term efficacy and safety data, emphasizing the need for robust clinical trials to establish optimal treatment protocols and comparative effectiveness against standard care. Future development is expected to advance along several interconnected, forward-looking directions, each with distinct technical bottlenecks. Biomimetic designs, inspired by natural structures, aim to enhance penetration and tissue interaction, yet reproducible and scalable fabrication of such complex micro-/nanoarchitectures with consistent mechanical performance remains challenging. Intelligent systems incorporating stimuli-responsive materials offer on-demand drug release, but ensuring specificity, sufficient sensitivity, and avoidance of off-target activation is nontrivial.

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Personalized medicine approaches seek to integrate AI and medical imaging to tailor treatments, yet achieving this requires seamless integration of rapid, accurate scar assessment with cost-effective, on-demand manufacturing workflows. Beyond scar suppression, the goal is to actively promote regeneration of skin appendages and restoration of normal tissue architecture, demanding unprecedented spatiotemporal control of multiple regenerative cues, including cells, growth factors, and scaffolds, to orchestrate complex morphogenesis. Additionally, integrating inorganic or polymeric nanoparticles into microneedles for enhanced targeting, imaging, or photothermal therapy presents a promising avenue, though their long-term biodistribution and safety in skin must be carefully evaluated. Taken together, these innovations hold great potential to transform microneedle patches from experimental tools into clinically effective therapies for HS, ultimately improving patient outcomes and quality of life.

Author contributions

Juntong Guo (Conceptualization [equal], Data curation [equal], Writing—original draft [equal]), Qinghan Tang (Conceptualization [equal], Data curation [equal], Writing—original draft [equal]), Zhengping Ge (Data curation [equal], Investigation [equal], Project administration [equal]), Qing Xia (Formal analysis [equal], Methodology [equal]), Huaikai Shi (Formal analysis [equal]), Jinlong Huang (Formal analysis [equal], Investigation [equal]), Xin Yan (Supervision [equal]), Chenxi Yang (Supervision [equal], Writing—review & editing [equal]), and Yiwei Wang (Data curation [equal], Funding acquisition [equal], Project administration [equal], Resources [equal], Supervision [lead], Writing—review & editing [lead])

Conflicts of interest

None declared.

Funding

This study was supported by the National Natural Science Foundation of China (No. 82372521, 82172217), the Natural Science Foundation of Nanjing University of Chinese Medicine (No. XZR2023071, China), Leading Program of Traditional Chinese Medicine First-class Discipline (ZYXYL2024-014), and Nanjing Key Medical Laboratory for Research on Chinese Medicine Preparations and Clinical Pharmacy Construction Project (NJSYXZDSYS-2023).

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Burns & Trauma, 2026, 14, tkag025
https://doi.org/10.1093/burnst/tkag025
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