

Ultrasound-Activated Piezocatalytic Microneedles Rescue Calcitonin Gene-Related Peptide-Dependent Neuroimmune Homeostasis to Promote Regeneration of Infected Diabetic Wounds

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2 Gene-Related Peptide-Dependent Neuroimmune Homeostasis to Promote
3 Regeneration of Infected Diabetic Wounds

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25 **Abstract**

26 Although chronic, infected diabetic wounds are characterized by disrupted
27 calcitonin gene-related peptide (CGRP)-driven neuroimmune signaling, CGRP
28 monotherapy fails to rescue infection-damaged cutaneous sensory nerves. Herein, we
29 develop protease-responsive hydrogel microneedles (termed ABC microneedles) that
30 integrate Au-decorated Bi₂S₃ piezocatalytic nanorods with neuropeptide CGRP. The
31 Au-Bi₂S₃ interface forms Schottky junctions that amplify ultrasound-triggered
32 piezocatalysis, thereby eliminating *S. aureus* biofilms, scavenging excess H₂O₂,
33 alleviating hypoxia, and consuming surplus glucose in the wound microenvironment.
34 *In vitro*, ultrasound-treated ABC microneedles protect fibroblasts and PC12 neuron-like
35 cells, restore neurite outgrowth, and trigger paracrine signals that promote endothelial
36 angiogenesis while dampening the excessive proinflammatory activation of myeloid
37 cells. In a mouse model of infected diabetic wounds, this combinatorial therapy
38 eradicates bacterial burden, restores cutaneous CGRP/transient receptor potential
39 vanilloid 1 signaling, activates vasculature-regenerative transcriptional programs, and
40 markedly accelerates wound closure. This study presents a synergistic strategy
41 targeting both infection and neuroimmune dysfunction to treat recalcitrant diabetic
42 wounds.

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44 **Keywords:** chronic infected diabetic wounds; Au-Bi₂S₃ piezocatalysis; microneedle;
45 calcitonin gene-related peptide; neuroimmune homeostasis.

1. Introduction

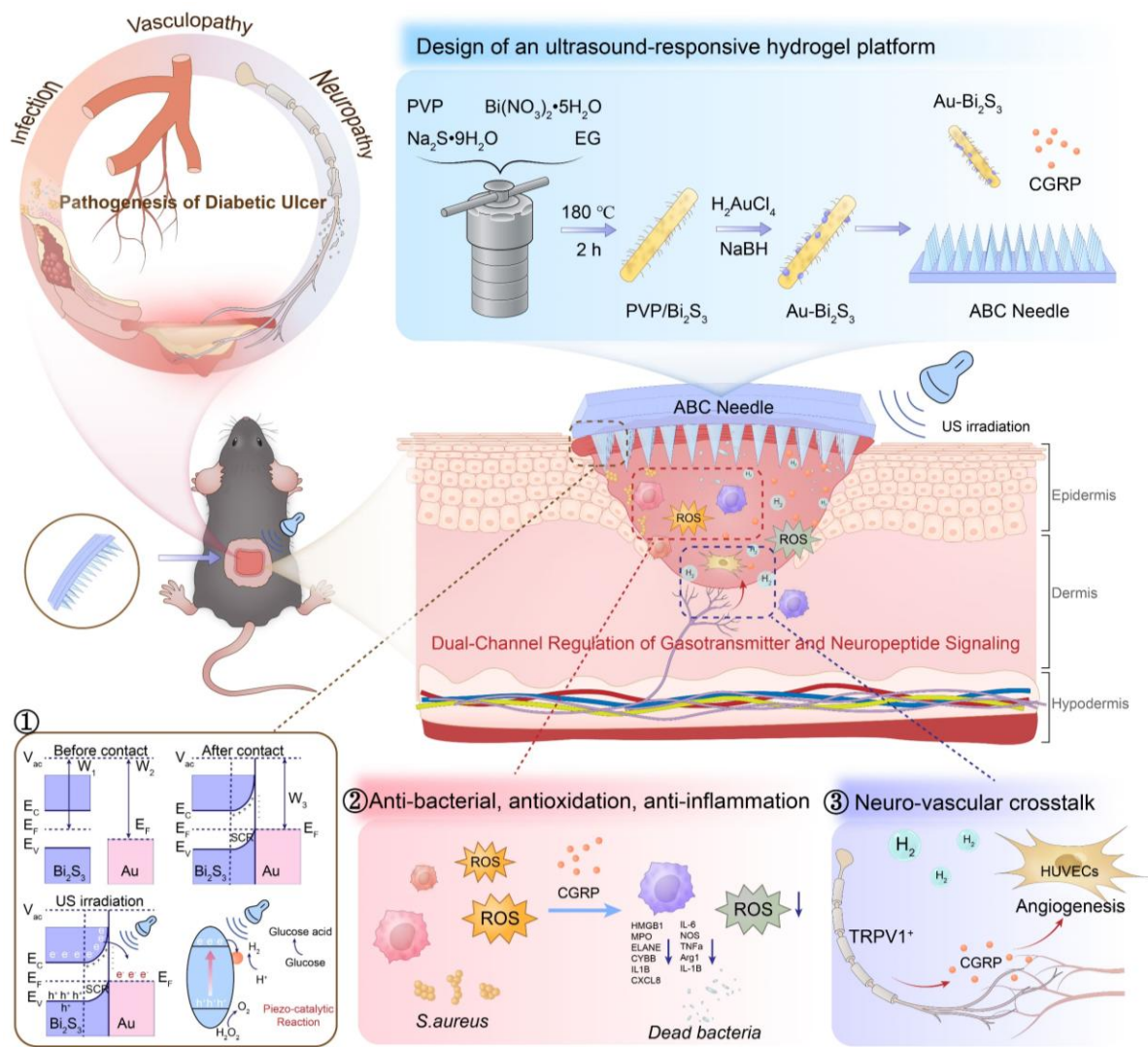
Chronic, infected diabetic wounds (IDWs), specifically diabetic foot ulcers (DFUs), remain a leading cause of amputation and impose a substantial clinical burden [1–3]. These wounds are locked in a self-reinforcing pathological cycle characterized by persistent bacterial infections, biofilm formation, impaired angiogenesis, tissue hypoxia, hyperglycemia, and excessive oxidative stress [4–6]. Moreover, *S. aureus* is frequently isolated from such lesions and can evade both antibiotics and host immunity by forming biofilms, ultimately driving chronic inflammation and tissue destruction [7]. Although conventional debridement, systemically administered antibiotics, and passive dressings can control contamination to some extent, they rarely correct the neurovascular and immune defects that underlie repair failure [8]. A therapeutic strategy that simultaneously addresses infections and restores damaged neuroimmune circuitry is therefore required.

Cutaneous sensory nerves are not merely sensory conduits; they actively regulate wound repair through the release of neuropeptides, such as calcitonin gene-related peptide (CGRP) [9–11]. CGRP acts on macrophages, keratinocytes, fibroblasts, and endothelial cells via the calcitonin receptor-like receptor (CALCRL)/receptor activity-modifying protein 1 (RAMP1) receptor complex and contributes to immune balance, angiogenesis, and re-epithelialization [12]. Transient receptor potential vanilloid 1 (TRPV1)-positive sensory neurons are a principal source of cutaneous CGRP, and their function is compromised in diabetes and further impaired by infections [13]. In non-healing diabetic wounds (DWs), loss of CGRP receptor competence in myeloid cells and accumulation of pro-inflammatory macrophage subsets coincide with impaired repair [14]. Although exogenous CGRP can partially shift macrophages toward a pro-repair phenotype, it fails to restore infection-damaged sensory nerve signals [15]. This limitation reflects the short half-life

and poor tissue retention of free peptides, as well as the fact that peptide supplementation alone does not remove the infectious and metabolic stressors that damage sensory nerve endings [16]. Restoring CGRP-dependent neuroimmune homeostasis therefore requires both infection control and sustained, wound-responsive CGRP delivery.

Ultrasound-responsive, piezocatalytic materials provide a strategy to overcome the infectious and metabolic barriers inherent to DWs [17–19]. Bi₂S₃ is a piezoelectric semiconductor whose mechanical deformation under ultrasound (US) generates separated charge carriers and reactive oxygen species, enabling antibacterial action and biofilm disruption [20]. Decoration with Au creates Schottky junctions at the Au–Bi₂S₃ interface, which promote interfacial charge transfer and suppress electron–hole recombination, thereby amplifying piezocatalytic activity [21–23]. Beyond bacterial killing, this catalytic process consumes excess H₂O₂, generates O₂, and oxidizes surplus glucose, collectively alleviating oxidative stress, hypoxia, and hyperglycemia in wound beds [24]. Microneedle arrays offer direct access to dermal wound compartments and bypass biofilm barriers, while protease-responsive hydrogel matrices allow payload release to be triggered by wound-site enzymes [25]. Integrating Au-Bi₂S₃ piezocatalysis with CGRP in such microneedle platforms could therefore couple antibacterial and microenvironment-remodeling effects with local neuropeptide restoration.

In this study, we engineered protease-responsive hydrogel microneedles (ABC microneedles) co-loaded with Au-Bi₂S₃ piezocatalytic nanorods and neuropeptide CGRP for the targeted treatment of IDWs (**Scheme 1**). Specifically, the heterostructured Au-Bi₂S₃ serves as an US-responsive piezocatalytic functional core, where the resulting Schottky junction significantly amplifies US-stimulated piezocatalytic effects. Consequently, this system efficiently eliminates *S. aureus* biofilms, scavenges excess H₂O₂, relieves wound hypoxia, and metabolizes redundant



Scheme 1. Schematic illustrating the preparation of ABC microneedles and ultrasound-powered synergistic therapy for infected diabetic wounds. The piezo-catalytic Au–Bi₂S₃ heterostructure provides antibacterial and antioxidative functions, while co-delivered calcitonin gene-related peptide reactivates neurovascular crosstalk to rescue sensory nerve function and promote angiogenesis. These components collectively achieve integrated microenvironment remodeling and neuroimmune regulation for chronic wound regeneration.

glucose to remodel the pathological microenvironment of DWs. The protease-sensitive hydrogel carrier enables the on-demand, sustained local release of neuropeptide CGRP in response to wound microenvironmental enzymes. This dual-functional design integrates microenvironment optimization and neuroimmune regulation; it eliminates the infectious and metabolic stressors that damage sensory nerves, while continuously released CGRP reactivates cutaneous neurovascular crosstalk, rescues impaired sensory nerve function, and drives endothelial angiogenesis. By combining these two core effects, the ABC microneedle platform achieves integrated wound microenvironment remodeling and neuroimmune homeostasis restoration, ultimately promoting the regeneration of refractory chronic DWs. We therefore performed both *in vitro* cell experiments and *in vivo* mouse model assays to systematically verify the therapeutic efficacy and the underlying molecular mechanism of this US-powered synergistic combinatorial strategy.

2. Results

2.1 Impaired CGRP-associated neuroimmune signaling defines human non-healing diabetic foot ulcers (DFUs)

To dissect the neuroimmune perturbations driving impaired repair in DWs, we analyzed single-cell transcriptomic profiles of human DFUs by stratifying patient samples into healthy skin, non-ulcerated diabetic tissues, healing DFUs (DFU-Hs), and non-healing DFUs (DFU-NHs). Myeloid cell subclustering resolved heterogeneous macrophage and dendritic-cell subsets across patient biopsies (Fig. 1a). Hallmark gene-set enrichment uncovered cell-type-specific transcriptional divergence between DFU-NHs and DFU-Hs, where interferon-driven signatures were strongly enriched in differentiated keratinocytes of DFU-NHs, whereas stromal and myeloid compartments from healing ulcers exhibited upregulation of programs controlling angiogenesis, epithelial-mesenchymal transitions, and tissue-restricted inflammatory signaling (Fig. 1b). These

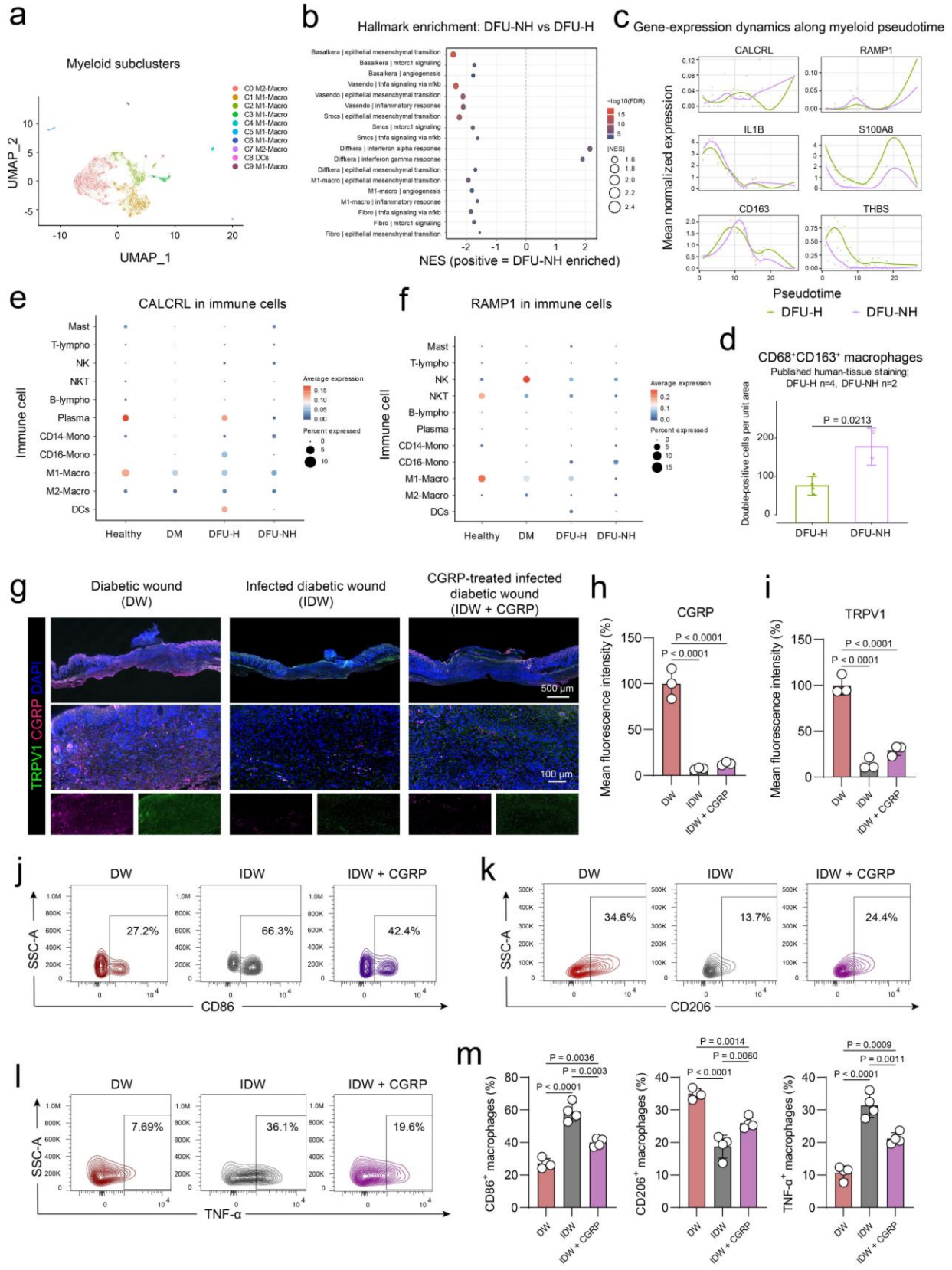


Fig. 1. Infection disrupts calcitonin gene-related peptide (CGRP)-dependent neuroimmune regulation in diabetic wounds. **a** Uniform manifold approximation and projection (UMAP) of myeloid cells from human diabetic foot ulcer (DFU) single-cell RNA-sequencing datasets, showing macrophage and dendritic-cell subclusters. **b** Hallmark gene-set enrichment analysis comparing non-healing (DFU-NH) with healing (DFU-H) DFUs. Positive normalized enrichment scores indicate pathways enriched in DFU-NH samples, while negative scores indicate pathways enriched in DFU-H samples. **c** Pseudotime-dependent expression of calcitonin receptor-like receptor (*CALCRL*), receptor activity-modifying protein 1 (*RAMP1*), *IL1B*, *SI00A8*, *CD163* and *THBS* in myeloid cells from DFU-H and DFU-NH samples. **d** Quantification of CD68⁺CD163⁺ macrophages in published human DFU-H and DFU-NH tissue samples. **e, f** Dot plots showing the expression of the CGRP receptor components *CALCRL* (**e**) and *RAMP1* (**f**) across immune-cell populations from healthy, diabetic, and healing or non-healing DFU samples. The dot size represents the proportion of expressing cells, while the color denotes average expression. **g** Representative immunofluorescence images of transient receptor potential vanilloid 1 (TRPV1) (green), CGRP (magenta) and nuclei (DAPI: blue) in DWs, infected diabetic wounds (IDWs), and CGRP-treated IDWs. **h, i** Quantification of **h** CGRP and **i** TRPV1 mean fluorescence intensities. **j–l** Representative flow-cytometric profiles of **j** CD86, **k** CD206, and **i** intracellular TNF- α in wound macrophages from the indicated groups. **m** Quantification of CD86⁺, CD206⁺, and NF- α ⁺ macrophages.

findings argue against a simplistic model of globally amplified inflammation in non-healing ulcers. Healing failure rather arises from aberrant partitioning of immune and reparative cell states, where keratinocyte-intrinsic interferon stress dominates, while pro-repair stromal-myeloid programs fail to engage effectively.

We next evaluated transcript abundance of *CALCRL* and *RAMPI*, encoding the two core subunits that assemble the functional CGRP receptor complex. In annotated M1-polarized macrophage populations, both genes displayed reduced average expression within the DFU-NH sample relative to healthy skin, with *RAMPI* showing a particularly marked downregulation in non-healing ulcer samples (**Fig. 1e,f**). Pseudo time trajectory reconstruction of myeloid differentiation further revealed that the physiological late-trajectory upregulation of *RAMPI* observed in DFU-H was substantially blunted in DFU-NH, while *CALCRL* followed a heterogeneous, non-monotonic expression profile across myeloid maturation (Fig. 1c). Consistent with this immune dysregulation, quantification of published human clinical tissue datasets demonstrated an increased abundance of CD68⁺CD163⁺ macrophages in DFU-NHs relative to DFU-Hs (Fig. 1d). Collectively, these human data indicate that the loss of CGRP receptor competence in myeloid cells coincides with the accumulation of this specific macrophage subset in non-healing clinical ulcers.

We extended these human observational findings to experimental mouse wounds to determine whether exogenous CGRP supplementation could reverse infection-driven neuroimmune defects. Three *in vivo* groups were compared: uninfected diabetic wounds (UDWs), IDWs, and IDWs treated with local CGRP delivery. Bacterial infection drastically diminished immunofluorescence signals for both CGRP and TRPV1; critically, even after exogenous CGRP supplementation, these neural marker signals never recovered to levels measured in UDWs (Fig. 1g–i). At the macrophage level, local CGRP delivery to IDWs reduced the frequencies of CD86⁺ pro-inflammatory and TNF- α ⁺ macrophages while expanding the CD206⁺ macrophage pool (Fig. 1j–m). These results reveal a key limitation of standalone CGRP therapy. Although exogenous peptides can partially remodel macrophage polarization toward a more pro-repair phenotype, they

cannot by themselves restore infection-damaged cutaneous sensory-nerve-associated signals. This behavior explains why peptide-only interventions yield incomplete therapeutic benefits for IDWs, highlighting the need for combinatorial strategies that simultaneously target infection and neuroimmune homeostasis.

2.2 Design and fabrication of CGRP-loaded Au-Bi₂S₃ composite microneedles

Given the incomplete rescue observed with isolated CGRP supplementation, we sought to build a combinatorial therapeutic platform that coupled local CGRP delivery with US-triggered catalytic antibacterial activity. To achieve this, we engineered hydrogel-based microneedles co-loaded with Au-decorated Bi₂S₃ and CGRP (ABC microneedles). Two comparator microneedle formulations were generated for benchmarking: BC microneedles containing Bi₂S₃ plus CGRP, and C microneedles loaded solely with CGRP (Scheme 1, Fig. 2a). Fabrication began with the synthesis of PVP-stabilized Bi₂S₃ nanorods, followed by *in situ* Au nanoparticle deposition onto nanorod surfaces; the resulting Au-Bi₂S₃ composite was then mixed with CGRP for microneedle casting. Transmission electron microscopy validated the rod-shaped morphology of bare Bi₂S₃, while Au-decorated nanorods exhibited abundant electron-dense granular deposits corresponding to immobilized Au nanoparticles (Fig. 2b–d). Energy-dispersive X-ray spectroscopy (EDS) elemental mapping confirmed the uniform distribution of Bi and S across the nanorod backbone and verified successful surface functionalization with Au (Fig. 2e). Hydrodynamic size measurements revealed largely overlapping submicrometer particle size distributions for bare Bi₂S₃ and Au-Bi₂S₃, indicating that Au decoration does not induce major particle aggregation (Fig. 2f). By contrast, surface zeta potential shifted from positive for bare Bi₂S₃ particles to negative for Au-Bi₂S₃ composite particles (Fig. 2g); this surface charge inversion is biologically relevant

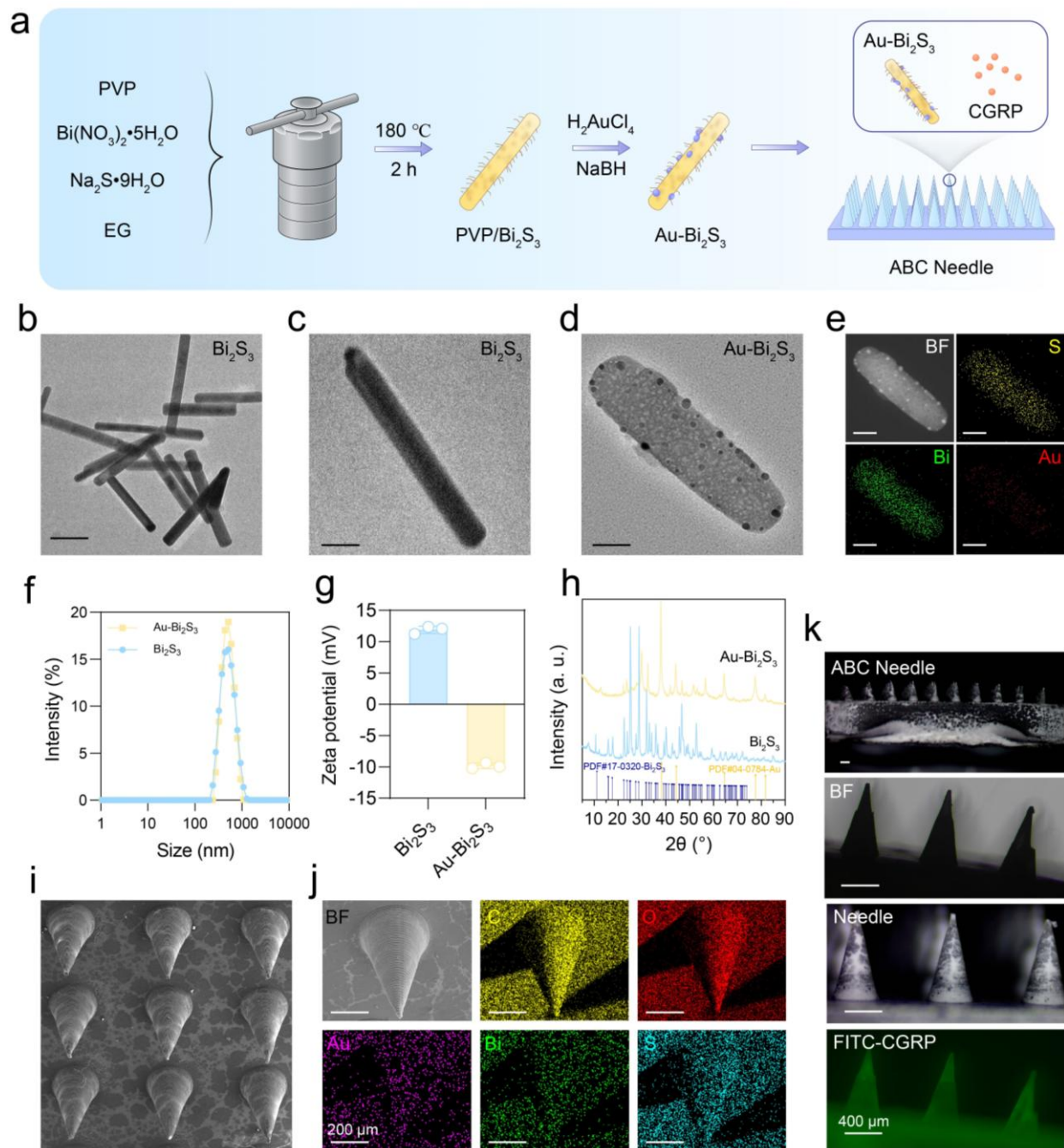


Fig. 2. Fabrication and physicochemical characterization of ABC microneedles. **a** Schematic illustration of ABC microneedle fabrication. Bi_2S_3 nanorods were decorated with Au through HAuCl_4 reduction, followed by the incorporation of Au- Bi_2S_3 nanoparticles and calcitonin gene-related peptide (CGRP) into a polyvinylpyrrolidone-based microneedle matrix. **b**, **c** Transmission electron microscopy (TEM) images of Bi_2S_3 nanorods at **(b)** low and **(c)** high

magnification. **d** TEM images of Au-Bi₂S₃ nanorods. **e** Bright-field TEM images and corresponding energy-dispersive X-ray spectroscopy (EDS) elemental maps of S, Bi, and Au in Au-Bi₂S₃. **f** Hydrodynamic particle size distributions of Bi₂S₃ and Au-Bi₂S₃ nanoparticles. **g** Zeta potentials of Bi₂S₃ and Au-Bi₂S₃ nanoparticles. **h** X-ray diffraction patterns of Bi₂S₃ and Au-Bi₂S₃, along with the reference diffraction pattern. **i** Scanning electron microscopy image of the microneedle array. **j** Bright-field images and corresponding EDS maps of C, O, Au, Bi, and S in an individual ABC microneedle. **k** Macroscopic and bright-field images of the ABC microneedle patch and fluorescence images showing the distribution of fluorescently labeled CGRP within the microneedles. Scale bars are shown in the corresponding panels.

because it influences particle interactions with bacterial and host cell membranes. X-ray diffraction patterns of Au-Bi₂S₃ retained all characteristic lattice reflections of Bi₂S₃ alongside additional peaks assignable to metallic Au, providing solid crystallographic evidence for composite formation (Fig. 2h). Supplementary elemental spectroscopy and X-ray photoelectron spectroscopy further confirmed the chemical composition of the material (Fig. S1).

Scanning electron microscopy and bright-field imaging confirmed the presence of highly ordered microneedle arrays with sharp, well-defined tips suitable for skin penetration (Figs. 2i,k and S2). EDS elemental mapping of individual ABC microneedles revealed that Au, Bi, and S were distributed throughout the carbon-and oxygen-rich hydrogel matrix, confirming the successful incorporation and homogeneous dispersion of the inorganic composite within the microneedle body (Fig. 2j). Fluorescence imaging of fluorescein isothiocyanate-labeled CGRP demonstrated uniform peptide distribution across the microneedle structures (Fig. 2k), demonstrating the efficient loading and optimal dispersion of the therapeutic peptide within the delivery platform. These physicochemical characterizations collectively confirm that the ABC

microneedle platform successfully integrates both the inorganic piezocatalytic components and the neuroregulatory peptide cargo.

2.3 Gold-functionalization potentiates US-driven piezocatalysis and protease-triggered peptide release

We next characterized the piezocatalytic performance of Au-Bi₂S₃ nanoparticles and validated the retention of catalytic function after integration into microneedles. Piezoresponse force microscopy measurements demonstrated voltage-dependent phase switching, with Au-Bi₂S₃ generating markedly larger piezoresponse amplitudes across the tested voltage window relative to bare Bi₂S₃ (Fig. S3). This enhancement is mechanistically attributed to the formation of Schottky junctions at Au-Bi₂S₃ interfaces, which facilitate charge separation upon US stimulation. Upon US irradiation, Au-Bi₂S₃ outperformed bare Bi₂S₃ and US-only controls across multiple catalytic readouts, driving robust time-dependent H₂O₂ scavenging, oxygen evolution, and hydrogen generation (Fig. 3a–e). These catalytic activities are functionally important for wound microenvironment remodeling: H₂O₂ decomposition mitigates oxidative stress, while local oxygen production alleviates the tissue hypoxia characteristics of DWs.

Crucially, these favorable catalytic functionalities were preserved following formulation into microneedles. Under identical US stimulations, ABC microneedles achieved significantly higher H₂O₂ elimination, oxygen release, and hydrogen production compared with BC and C microneedles (Fig. 3f–h). Gold modification also boosted glucose-oxidized product yields under US exposure; this trend was fully recapitulated for the complete ABC microneedle construct (Fig. 3i,j), indicating that the platform can metabolize excess glucose abundant within DW beds.

We further evaluated the microneedle degradation kinetics and peptide release behavior *in vitro*. ABC microneedles exhibited progressive mass loss across a 96 min incubation period;

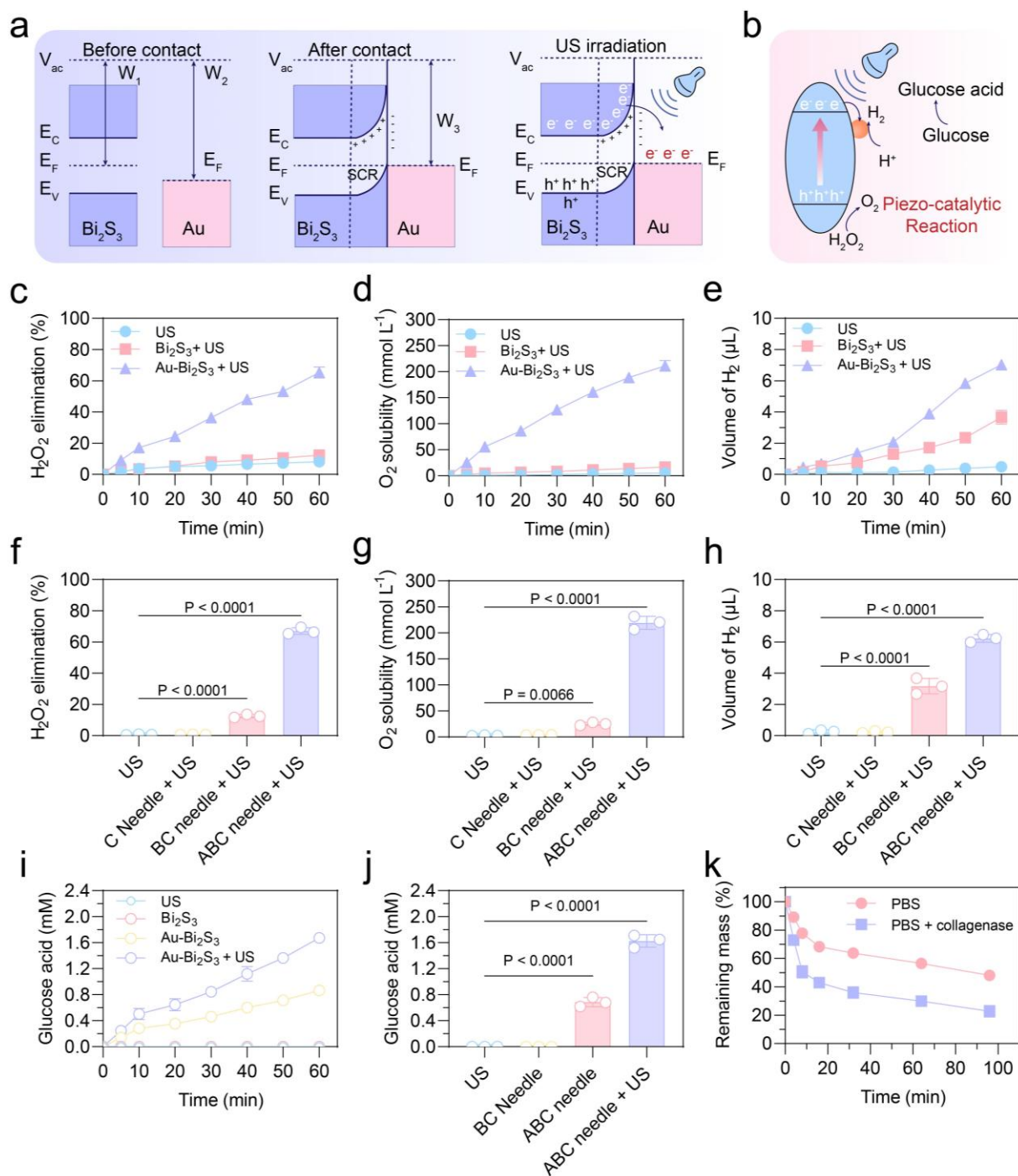


Fig. 3. Ultrasound enhances the catalytic activity of Au- Bi_2S_3 and controls microneedle-mediated release. **a** Schematic energy band diagrams of Bi_2S_3 and Au before contact, after formation of the Au- Bi_2S_3 Schottky interface and under ultrasound (US) stimulation, illustrating US-induced charge separation and interfacial electron transfer. **b** Proposed US-

activated catalytic pathways involving glucose oxidation, H_2O_2 consumption, and O_2 and H_2 generation. **c** Time-dependent H_2O_2 elimination in the US, Bi_2S_3 + US and Au- Bi_2S_3 + US groups. **d, e** Time-dependent changes in **d** dissolved O_2 and **e** H_2 production under the indicated conditions. **f–h** Endpoint comparison of **f** H_2O_2 elimination, **g** dissolved O_2 concentration, and **h** H_2 production among the US, C microneedle + US, BC microneedle + US, and ABC microneedle + US groups. **i** Time-dependent production of the glucose-oxidation product under the indicated material and US conditions. **j** Endpoint comparison of glucose-oxidation product formation among the US, BC microneedle, ABC microneedle, and ABC microneedle + US groups. **k** Residual mass of ABC microneedles incubated in phosphate-buffered saline (PBS) or PBS containing collagenase for up to 96 min.

degradation proceeded substantially faster in phosphate-buffered saline (PBS) supplemented with collagenase than in PBS alone (Fig. 3k). Consistently, cumulative CGRP release increased over time and was significantly augmented in a collagenase-containing medium mimicking wound-site protease activity (Fig. S4). These observations indicate that the ABC microneedle is responsive to wound-relevant proteases: as the hydrogel matrix degrades within wound tissue, therapeutic CGRP is liberated locally. These data collectively establish that the ABC platform achieves two core design goals: US-triggered piezocatalytic activity and protease-responsive on-site release of CGRP.

2.4 ABC-microneedle US therapy eliminates *S. aureus* biofilms and preserves fibroblast viability

We assessed the antibacterial potency of the ABC microneedle combined with US against *S. aureus*, a major pathogen driving infection-associated DFU-NHs. Scanning electron microscopy revealed severe disruption of the bacterial surface architecture following ABC microneedle + US

treatment, while transmission electron microscopy further revealed compromised cell envelope integrity and a disorganized intracellular ultrastructure (Fig. 4a,b), consistent with the physical and chemical damage inflicted by piezocatalytic outputs. Quantification of colony-forming units demonstrated markedly suppressed bacterial viability in the ABC microneedle + US group compared with the untreated, US-only and BC microneedle + US controls (Fig. 4c,d).

Crystal-violet staining of mature biofilms revealed a substantial reduction in biofilm biomass upon ABC microneedle + US treatment (Fig. 4e). Three-dimensional confocal live/dead imaging confirmed an elevated fraction of dead bacteria and a reduced biofilm thickness, although residual biofilm material remained detectable post-treatment (Fig. 4g,h). This partial rather than complete biofilm eradication highlights that in complex biological settings, piezocatalytic therapy functions by reducing, rather than fully eliminating, embedded biofilm bacteria.

To model host cell injury during wound infection, we established an *in vitro* co-culture system of *S. aureus* and L929 fibroblasts to recapitulate the pathological crosstalk between invading bacteria and wound-resident stromal cells within IDW beds. Exposure of fibroblasts to viable *S. aureus* imposed substantial cytotoxic stress. This bacterial challenge strongly suppressed fibroblast proliferative capacity, as evidenced by markedly diminished 5-ethynyl-2'-deoxyuridine (EdU) incorporation (a marker of active DNA replication and cell cycle progression) while simultaneously driving elevated host cell death. Such loss of fibroblast viability and proliferative function can directly impede granulation tissue formation and matrix deposition, two key processes required for cutaneous wound closure. Relative to infected untreated, US-only, and BC microneedle + US comparator conditions, ABC microneedle + US treatment significantly restored the fraction of EdU-positive proliferative fibroblasts and preserved a substantially larger

population of viable L929 cells (Fig. 4i–l). These *in vitro* observations demonstrate that the combinatorial treatment exerts desirable selective bioactivity: it inflicts structural damage and

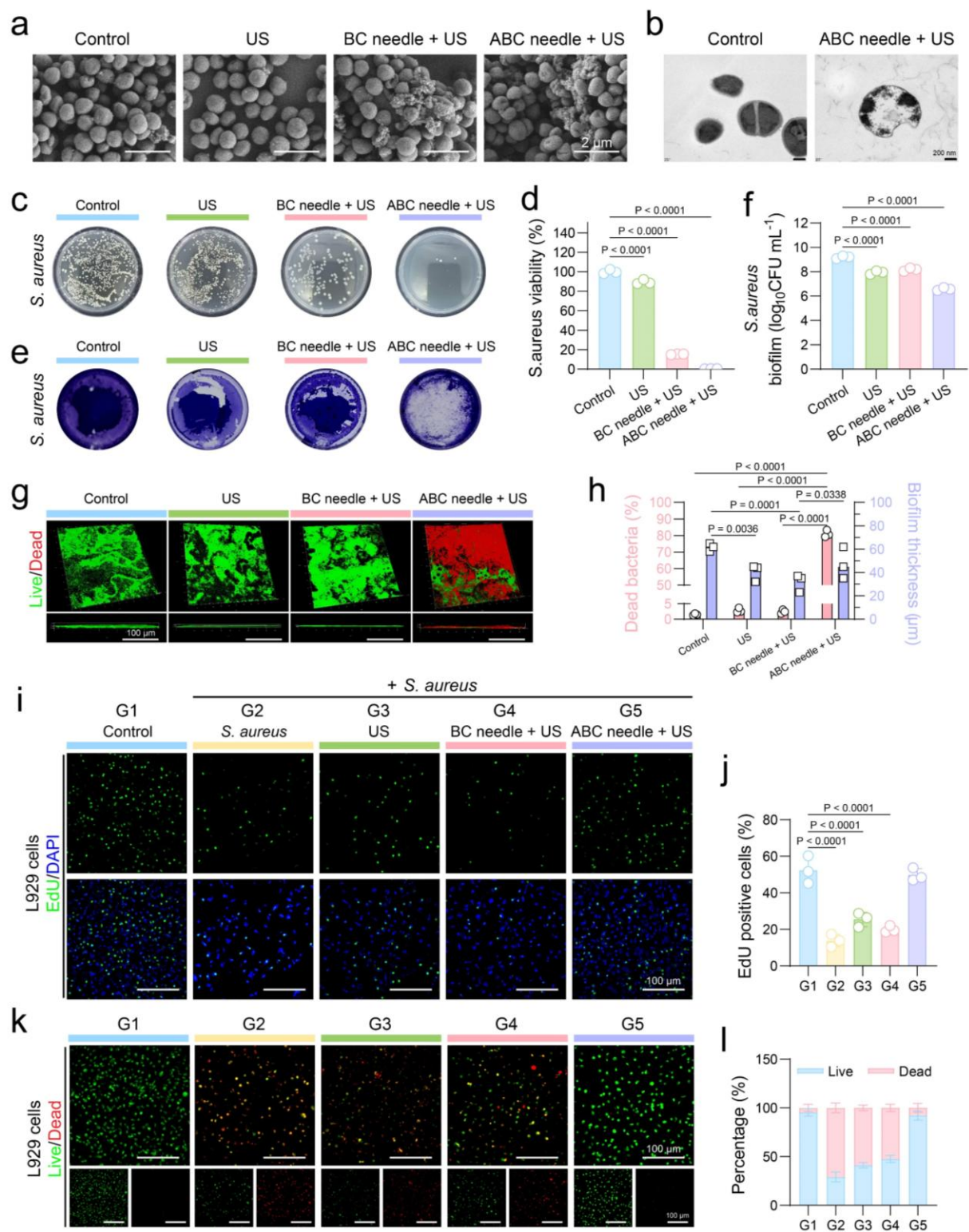


Fig. 4. ABC microneedles eradicate *Staphylococcus aureus* and protect fibroblasts from infection-associated injury. **a** Scanning electron microscopy images of *S. aureus* following the indicated treatments. **b** Transmission electron microscopy images showing the ultrastructure of untreated bacteria and bacteria treated with ABC microneedle + ultrasound (US). **c** Representative agar plates of viable *S. aureus* recovered following treatment. **d** Quantification of bacterial viability. **e** Representative crystal-violet-stained *S. aureus* biofilms following treatment. **f** Quantification of the residual biofilm-associated bacterial burden. **g** Representative three-dimensional confocal images of live/dead-stained *S. aureus* biofilms. **h** Quantification of dead bacteria and biofilm thickness. **i** Representative 5-ethynyl-2'-deoxyuridine (EdU) staining of L929 fibroblasts in the bacteria–fibroblast co-culture model (EdU, green; DAPI: blue). **j** Quantification of EdU-positive L929 cells. **k** Representative live/dead fluorescence images of L929 cells following the indicated treatments. **l** Quantification of viable and dead L929 cells. Groups are defined as G1, untreated control; G2, *S. aureus*; G3, *S. aureus* + US; G4, *S. aureus* + BC microneedle + US; and G5, *S. aureus* + ABC microneedle + US. Scale bars are shown in the corresponding panels.

reduces the viability of pathogenic *S. aureus* while concurrently mitigating infection-triggered cytotoxicity toward wound-resident fibroblasts. The capacity to safeguard stromal cell function in the face of bacterial insult represents an important prerequisite for successful downstream tissue regeneration because sustained fibroblast survival and proliferation are essential for granulation tissue build-up, extracellular matrix production, and subsequent wound bed remodeling.

2.5 ABC-microneedle-US rescues neuron-like cell dysfunction induced by bacterial insult

Diabetic wound healing failure is tightly linked to peripheral sensory nerve damage and the loss of neuropeptide signaling. We utilized an *S. aureus*-PC12 neuron-like cell co-culture system

to model infection-mediated neuronal injury. Bacterial exposure caused a pronounced loss of β -tubulin-positive neurite networks and reduced CGRP immunofluorescence signal. Compared with infected, untreated, or US-treated cultures, ABC microneedle + US significantly restored neurite outgrowth and CGRP signal intensity, producing more extensive neurite arborization than BC microneedle + US (Fig. 5a–c). These morphological improvements suggest that combinatorial treatment can reverse infection-driven neuron-like cell dysfunction.

The recovery of neuronal morphology was accompanied by improved cell survival and restored mitochondrial homeostasis, which is a key driver of neuronal fitness. Annexin V/propidium iodide flow cytometry revealed reduced apoptotic rates in the ABC microneedle + US group compared with all infected comparator conditions (Fig. 5d,e). Moreover, JC-1 staining revealed the recovery of the aggregate-to-monomer fluorescence ratio, indicative of restored mitochondrial membrane potential (Fig. 5f,g). In line with this finding, the proportion of MitoSOX-positive cells accumulating mitochondrial superoxide was decreased following ABC microneedle + US treatment (Fig. S5). Collectively, these data indicate that ABC microneedle + US mitigates infection-provoked mitochondrial damage and limits apoptotic cell death in neuron-like cells.

Bulk RNA sequencing was performed to obtain transcriptome-wide insights into PC12 cellular responses. Applying standard differential-expression thresholds, 698 genes were upregulated and 534 genes downregulated in ABC microneedle + US treated cells relative to *S. aureus*-exposed cultures (Fig. 5h). Unsupervised clustering separated infection-associated transcriptional signatures, showing partial reversion toward the uninfected control state alongside treatment-specific gene expression programs (Figs. 5i and S6). Whereas bacterial challenge

342 induced 1340 differentially expressed genes relative to uninfected controls, only 122 differentially
343 regulated genes persisted after the ABC microneedle + US intervention (Fig. S7). This large

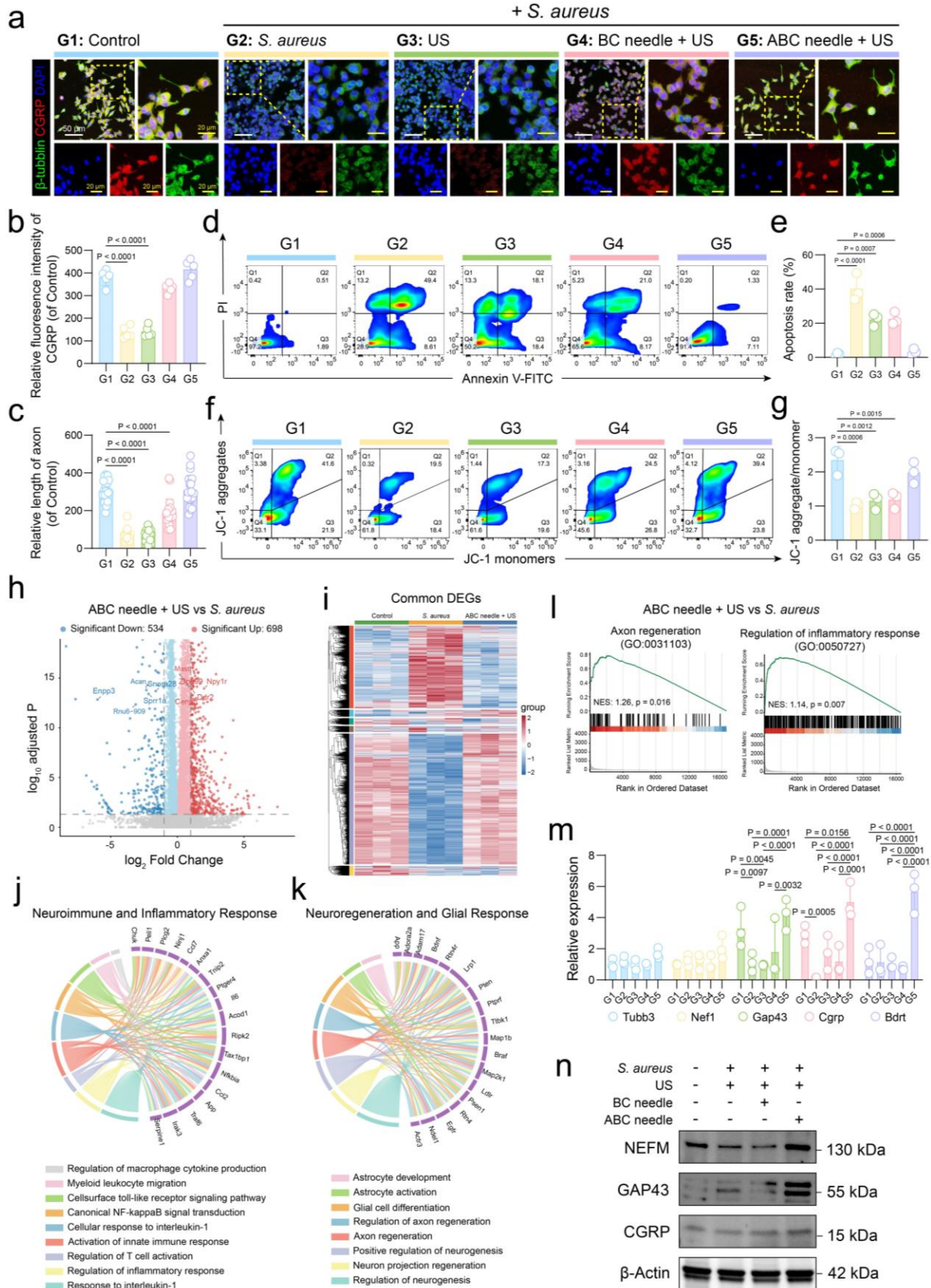


Fig. 5. ABC microneedle treatment protects PC12 cells and restores infection-impaired neuronal features. **a** Representative immunofluorescence images of β -tubulin (green), calcitonin gene-related peptide (CGRP; red) and nuclei (DAPI; blue) in PC12 cells from the indicated groups. Enlarged images correspond to the boxed regions. **b, c** Quantification of **b** relative CGRP fluorescence intensity and **c** β -tubulin-positive neurite length. **d** Representative Annexin V–fluorescein isothiocyanate/propidium iodide flow-cytometric profiles of PC12 cell apoptosis. **e** Quantification of apoptotic cells. **f** Representative JC-1 flow-cytometric analysis of mitochondrial membrane potential. **g** Quantification of the JC-1 aggregate-to-monomer fluorescence ratio. **h** Volcano plot of differentially expressed genes between the ABC microneedle + ultrasound (US) and *S. aureus* groups. Red and blue indicate significantly upregulated and downregulated genes, respectively. **i** Heatmap of common differentially expressed genes in the control, *S. aureus*, and ABC microneedle + US groups. **j, k** Chord diagrams linking differentially expressed genes to biological processes associated with **j** neuroimmune and inflammatory regulation and **k** neuroregeneration and glial responses. **l** Gene-set enrichment analysis of axon regeneration and regulation of the inflammatory response in ABC microneedle + US-treated cells relative to *S. aureus*-exposed cells. **m** Reverse transcription-quantitative polymerase chain reaction analysis of *Tubb3*, *Nefl*, *Gap43*, *Cgrp*, and *Bdrt* in PC12 cells. **n** Representative immunoblots of NEFM, GAP43, and CGRP in PC12 cells under the four indicated conditions; β -actin served as the loading control. Groups are defined as G1, untreated control; G2, *S. aureus*; G3, *S. aureus* + US; G4, *S. aureus* + BC microneedle + US; and G5, *S. aureus* + ABC microneedle + US.

reduction in transcriptional perturbation suggests that the treatment largely normalized the infection-disturbed transcriptome.

Functional annotation linked these transcriptional shifts to the modulation of inflammatory signaling, neuroimmune crosstalk, and neuronal projection regeneration pathways (Figs. 5j,k). Gene-set enrichment analysis (GSEA) revealed significant enrichment for axon regeneration (Normalized enrichment score (NES) = 1.26; $P = 0.016$) and regulation of inflammatory response (NES = 1.14; $P = 0.007$) in ABC microneedle + US treated versus infected PC12 cells (Fig. 5l). Notably, the “regulation of inflammatory response” gene set encompasses both pro- and anti-inflammatory programs and does not inherently specify the directionality of inflammatory change.

Reverse transcription-quantitative polymerase chain reaction analysis confirmed the restored transcript abundance of *Cgrp* and significant upregulation of the neurite-outgrowth marker *Gap43* in the ABC microneedle + US group; by comparison, *Tubb3* and neurofilament-encoding transcripts exhibited only modest changes (Fig. 5m). Immunoblotting further demonstrated elevated NEFM, GAP43, and CGRP protein levels in ABC microneedle + US samples relative to infected reference groups (Figs. 5n and S8). These assays document the restoration of a CGRP-rich neuron-like phenotype, but they cannot formally distinguish peptide originating from microneedle delivery versus endogenous cellular synthesis, nor do they directly quantify sustained endogenous CGRP secretion.

2.6 Paracrine mediators from treated neuron-like cells modulate endothelial and myeloid cell function

Within wound microenvironments, sensory-neuron-derived mediators exert paracrine control over multiple wound-repair cell types. We therefore tested to determine whether soluble factors released by treated PC12 neuron-like cells could propagate therapeutic effects to endothelial and myeloid cells. The conditioned medium was harvested from bacteria-challenged and treated PC12

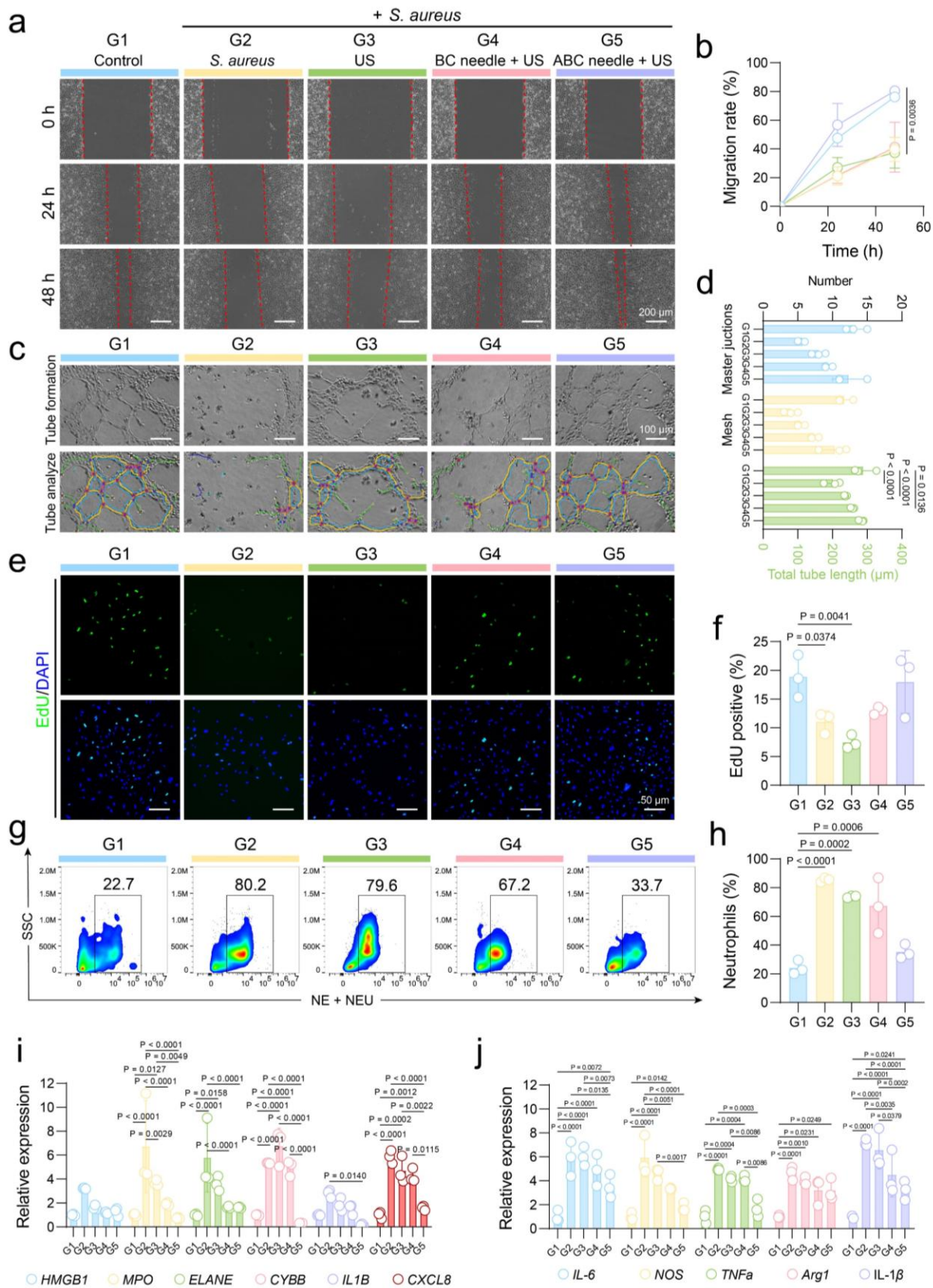


Fig. 6. Signals released by treated PC12 cells regulate endothelial and innate immune-cell responses.

Conditioned media were collected from PC12 cells subjected to the indicated bacteria and microneedle treatments and clarified by centrifugation before transfer to recipient cells.

a Representative image of human umbilical vein endothelial cell (HUVEC) scratch-wound assays at 0, 24 and 48 h following exposure to PC12-conditioned media. **b** Quantification of HUVEC

migration. **c** Representative images and image-analysis overlays of HUVEC tube formation. **d** Quantification of master junctions, mesh number, and total tube length. **e** Representative 5-

ethynyl-2'-deoxyuridine (EdU) staining of HUVECs (EdU, green; DAPI: blue). **f** Quantification of EdU-positive HUVECs. **g** Representative flow-cytometric plots of the gated neutrophil

population following exposure to PC12 cell-conditioned media. **h** Quantification of the gated neutrophil population. **i** Reverse transcription-quantitative polymerase chain reaction (RT-qPCR)

analysis of neutrophil-associated inflammatory and antimicrobial genes, including *HMGB1*, *MPO*, *ELANE*, *CYBB*, *IL1B*, and *CXCL8*. **j** RT-qPCR analysis of macrophage-associated inflammatory

and regulatory genes, including *IL6*, *NOS*, *TNF*, *ARG1*, and *IL1B*. Groups are defined according to the treatment applied during PC12-conditioned-medium generation: G1, untreated control; G2,

S. aureus; G3, *S. aureus* + ultrasound (US); G4, *S. aureus* + BC microneedle + US; and G5, *S. aureus* + ABC microneedle + US. Scale bars are shown in the corresponding panels.

cultures, clarified by centrifugation to remove cellular debris and transferred onto recipient cell cultures. Human umbilical vein endothelial cells (HUVECs) cultured in conditioned medium from

ABC microneedle + US-treated PC12 cells exhibited accelerated scratch closure at both 24 and 48 h compared with HUVECs receiving medium from infected or incompletely treated PC12

cultures (Fig. 6a,b).

Tube-formation assays revealed the recovery of angiogenic network characteristics, including master junction count, mesh formation, and total tube length (Fig. 6c,d). EdU staining also demonstrated high proliferative activity in HUVECs exposed to the ABC microneedle + US-derived conditioned medium (Fig. 6e,f). These results indicate that soluble mediators from treated neuron-like cells promote endothelial proliferation and angiogenic capacity, which is critical for the revascularization of poorly perfused DWs.

The functional phenotypes of myeloid cells were modulated by PC12-derived soluble signals. In neutrophil cultures, exposure to the ABC microneedle + US conditioned medium reduced the abundance of the gated neutrophil population relative to the infected, US-only, and BC microneedle + US counterparts (Fig. 6g,h). Transcript levels of pro-inflammatory and effector genes HMGB1, MPO, ELANE, CYBB, IL1B, and CXCL8 were significantly downregulated (Fig. 6i). Although these transcript measurements reflect reduced neutrophil pro-inflammatory priming, they do not directly quantify neutrophil extracellular trap formation.

In macrophages, conditioned medium from ABC microneedle + US-treated PC12 cells lowered the mRNA levels of the key pro-inflammatory mediators *Il-6*, *Nos*, *Tnf- α* , and *Il-1 β* relative to the medium derived from infected PC12 cells. Notably, *Arg1*, a canonical marker of M2-like polarization, was not influenced by this treatment (Fig. 6j). This observation is biologically meaningful because it demonstrates that the paracrine signal drives the selective suppression of pro-inflammatory gene expression rather than complete, broad-spectrum M2-type macrophage reprogramming. Although supernatant clarification removes cellular debris, it does not eliminate soluble CGRP originally released from the microneedles. Consequently, this experimental setup does not definitively isolate the specific contribution of PC12-synthesized CGRP to the observed paracrine effects.

2.7 ABC-microneedle-US treatment accelerates the closure of *S. aureus*-IDWs *in vivo*

We next performed an *in vivo* therapeutic evaluation using a well-established mouse model of *S. aureus*-IDWs. The experimental groups included untreated controls, US alone, and BC microneedle + US, non-activated ABC microneedle, and ABC microneedle + US. Serial wound imaging and area quantification over the 14-day experimental window revealed the fastest healing kinetics in the ABC microneedle + US cohort, achieving near-complete wound closure by day 14 and outperforming both the non-activated ABC microneedle and BC microneedle + US controls (Figs. 7a,c and S9). These *in vivo* outcomes confirm that both the Au Bi₂S₃ piezocatalytic component and US activation are required for maximal therapeutic benefit.

Quantitative culture of the excised wound tissue demonstrated the lowest residual *S. aureus* bacterial burden in animals treated with ABC microneedle + US (Fig. 7b,d). Giemsa histology consistently displayed markedly reduced bacterial deposits within the wound tissue sections, with maximal bacterial clearance observed in the ABC microneedle + US group across the assessed time points (Fig. 7i,j). Hematoxylin and eosin staining on days 3 and 10 showed progressive re-epithelialization following ABC microneedle + US therapy, accompanied by reduced epidermal hyperthickening on day 10 (Fig. 7e,f), consistent with the resolution of wound-site inflammation. Furthermore, Masson's trichrome staining revealed collagen deposition and wound bed bridging, where the residual wound length was minimal in the ABC microneedle + US group on day 10 (Fig. 7g,h). Collectively, these *in vivo* data establish that ABC microneedle + US improves macroscopic wound closure, facilitates bacterial clearance, and drives histological tissue repair within the 14-day observation window.

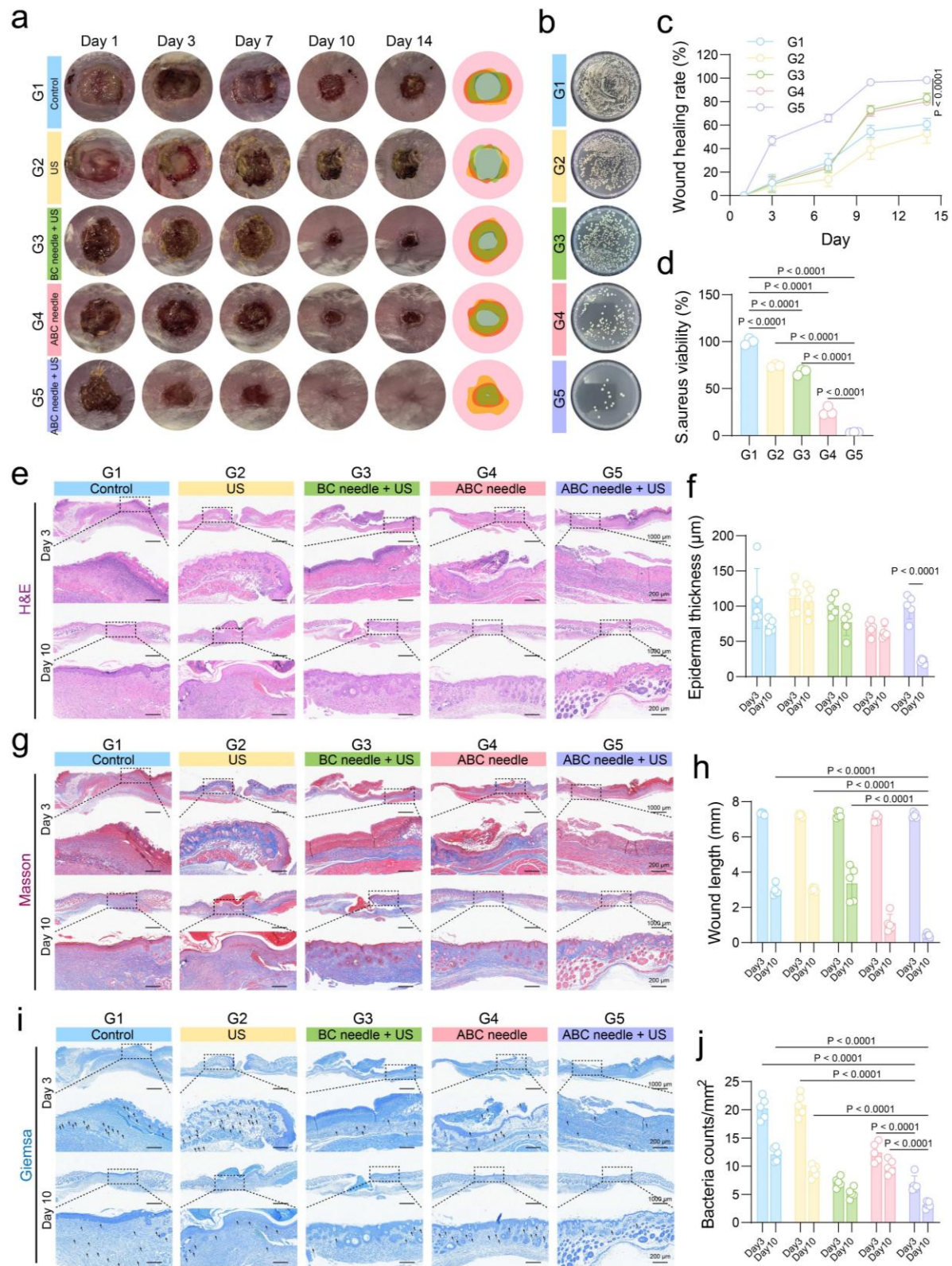


Fig. 7. ABC microneedles reduce bacterial burden and accelerate infected diabetic wound repair *in vivo*. **a** Representative photographs and wound-area tracings of infected diabetic wounds on days 1, 3, 7, 10, and 14 post-treatment. **b** Representative agar plates showing viable *S. aureus* recovered from wound tissues. **c** Quantification of wound-healing rates over time. **d** Quantification of viable *S. aureus* recovered from wound tissues. **e** Representative hematoxylin and eosin-stained wound sections on days 3 and 10. **f** Quantification of epidermal thickness. **g** Representative Masson's trichrome-stained wound sections on days 3 and 10. **h** Quantification of residual wound length. **i** Representative Giemsa-stained wound sections on days 3 and 10, with arrows indicating bacteria within the wound tissue. **j** Quantification of tissue-associated bacteria per unit area. Groups are defined as control, ultrasound (US), BC microneedle + US, ABC microneedle, and ABC microneedle + US. Scale bars are shown in the corresponding panels.

2.8 Restored neuropeptide signaling and transcriptomic reprogramming underpin therapeutic responses in wounds

To establish whether enhanced *in vivo* tissue repair correlated with the recovery of cutaneous neural signaling, we analyzed CGRP and TRPV1 immunofluorescence in wound tissue sections. The ABC microneedle + US treatment significantly increased CGRP and TRPV1 fluorescence intensities relative to those in untreated wounds and all comparator intervention groups (Fig. 8a–c). Wide-field imaging revealed a broad spatial distribution of these neuropeptide and ion channel signals across the wound bed (Fig. S10). However, important interpretive caveats remain: increased fluorescence intensity alone cannot distinguish exogenously delivered CGRP from endogenously produced neuropeptides, nor does it formally prove the expansion of sensory neuron populations within the wound tissue. Concurrently, color-coded Doppler US imaging revealed enhanced vascular signals at the wound-site in the ABC microneedle + US group, with the most

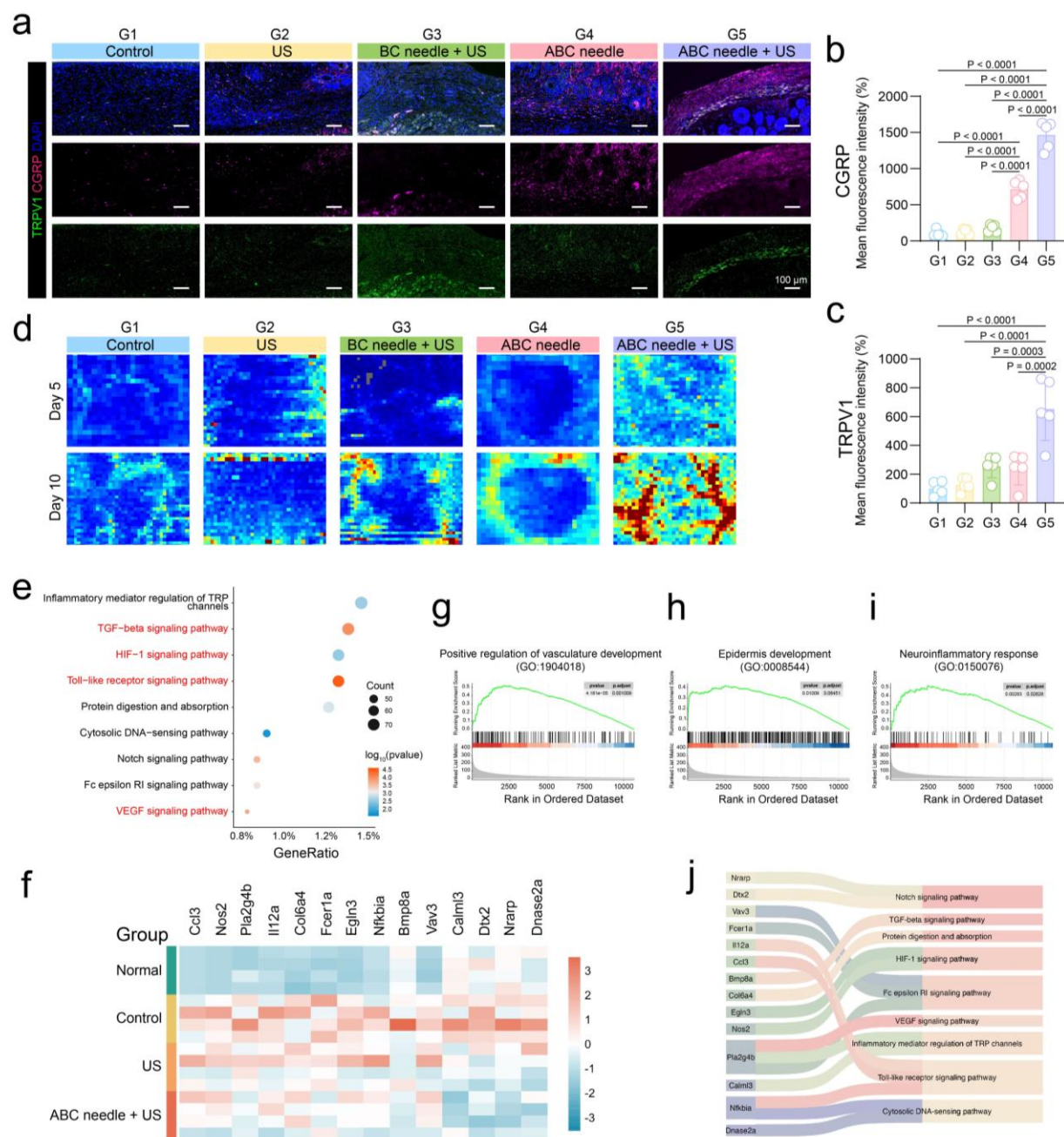


Fig. 8. ABC microneedles restore cutaneous sensory neuropeptide signals and activate regenerative programs in infected diabetic wounds. **a** Representative immunofluorescence images of transient receptor potential vanilloid 1 (TRPV1; green), calcitonin gene-related peptide (CGRP; magenta), and nuclei (DAPI; blue) in wound tissues obtained from the indicated groups. **b, c** Quantification of **b** CGRP and **c** TRPV1 mean fluorescence intensities. **d** Representative color

Doppler ultrasound (US) images of wound-associated blood flow on days 5 and 10 post-treatment. **e** Kyoto Encyclopedia of Genes and Genomes pathway-enrichment analysis of differentially expressed genes in wound tissues. The bubble size represents the number of enriched genes, while the color indicates enrichment significance. **f** Heatmap showing representative differentially expressed genes related to inflammatory regulation, extracellular-matrix remodeling, hypoxia responses, Notch signaling, and vascular regulation in normal skin alongside wounds from the control, US and ABC microneedle + US groups. **g–i** Gene-set enrichment analysis of **g** positive regulation of vasculature development, **h** epidermis development, and **i** neuroinflammatory response in wound tissues for the indicated ranked comparison. **j** Sankey diagram linking representative differentially expressed genes to enriched biological pathways. Groups are defined as control, US, BC microneedle + US, ABC microneedle and ABC microneedle + US.

prominent differences observed on Day 10 (Fig. 8d). Notably, these US observations remain qualitative because the imaging modality lacks the capacity for rigorous quantitative vascular metrics.

Bulk RNA-sequencing of diabetic wound tissue uncovered treatment-dependent transcriptional reprogramming across multiple key pathways, including TGF- β , HIF-1, Toll-like receptor, VEGF, and TRP-channel signaling (Fig. 8e,f,j). Sample-wise gene-expression clustering identified distinct transcript modules for normal skin, untreated wounds, US-treated wounds, and ABC microneedle + US-treated wounds; rather than a simple full reversion to the homeostatic skin transcriptome, treatment drives the establishment of a unique repair-oriented transcriptional state (Fig. S11). GSEA demonstrated significant enrichment for positive regulation of vasculature development (adjusted $P = 0.001009$) and neuroinflammatory response (adjusted $P = 0.02628$); the gene set for epidermal development did not meet the adjusted $P < 0.05$ significance threshold

(adjusted $P = 0.06451$) (Fig. 8g–i). This failure implies that the treatment preferentially activates vascular and neuroinflammatory regulatory programs, whereas epidermal developmental pathways remain incompletely restored.

Collectively, the *in vitro* and *in vivo* results showed that ABC microneedle + US achieves multimodal therapeutic outputs: antibacterial activity against wound-associated pathogens; enhanced neuron-like cell function and mitochondrial homeostasis; paracrine modulation of endothelial and myeloid cell behavior; and accelerated healing of IDWs. The concomitant upregulation of CGRP/TRPV1-associated signals and large-scale transcriptomic remodeling supports our proposed neuroimmune-centered therapeutic framework. Nevertheless, these correlative observations do not formally establish a strict causal dependence on intact CGRP pathway signaling, which would require targeted genetic or pharmacological loss-of-function experiments in future studies.

3. Discussion and conclusion

Chronic IDWs represent an intractable clinical challenge driven by the synergistic deterioration of bacterial infection, disordered microenvironment metabolism, and defective neuroimmune crosstalk [7,26]. Consistent with previous clinical transcriptomic evidence, the present study verified that DFU-NHs exhibit prominent downregulation of CGRP receptor subunits in myeloid cells, accompanied by an abnormal accumulation of pro-inflammatory macrophage subsets [27–29]. Bacterial infection further disrupts cutaneous TRPV1/neuropeptide CGRP signaling, forming a vicious cycle of persistent inflammation and impaired tissue regeneration [30–32]. Notably, although standalone CGRP supplementation only modulates macrophage polarization partially, it fails to rescue infection-damaged sensory nerve function, which fundamentally limits the therapeutic efficacy of a single neuroregulatory intervention for

IDWs. These findings highlight that dual targeting of bacterial infection and CGRP-mediated neuroimmune homeostasis remains an essential prerequisite for the effective repair of refractory DWs.

To address this unmet therapeutic demand, we successfully constructed a protease-responsive ABC microneedle platform integrating Au-modified Bi₂S₃ piezocatalytic nanorods and neuropeptide CGRP. Benefiting from the Schottky junction formed at the Au–Bi₂S₃ interface, the composite nanomaterial effectively inhibits electron–hole recombination and significantly enhances US-triggered piezocatalytic performance. Upon ultrasonic irradiation, the ABC microneedles efficiently eradicate *S. aureus* biofilms, scavenge excessive intracellular and extracellular H₂O₂, relieve wound hypoxia, and metabolize redundant glucose in the wound microenvironment. This multifaceted action successfully reverses the typical high-oxidative-stress, hypoxic, and hyperglycemic pathological niche of DWs. Moreover, the hydrogel microneedle matrix achieves spatiotemporally controllable CGRP release in response to wound-derived protease activity, realizing localized and sustained neuroimmune regulation while overcoming the shortcomings of a short half-life and low bioavailability inherent to free CGRP.

In vitro functional experiments systematically validated the multimodal therapeutic advantages of the ABC microneedle + US synergistic strategy. The combinatorial treatment exhibits excellent biosafety toward wound-resident fibroblasts while efficiently eradicating pathogenic bacteria, thereby resolving the common dilemma of conventional antibacterial therapies that inadvertently damage normal host cells. In *S. aureus*-challenged PC12 neuron-like cells, ABC microneedle-mediated piezocatalysis and CGRP delivery synergistically alleviate mitochondrial damage and cellular apoptosis, restore neurite outgrowth and endogenous CGRP expression, and fundamentally rescue infection-induced neuronal dysfunction. Further paracrine

mechanism studies confirmed that these repaired neuron-like cells secrete soluble regulatory mediators to promote endothelial cell proliferation and angiogenesis while selectively suppressing the pro-inflammatory activation of neutrophils and macrophages. In contrast to traditional M2 macrophage polarization therapies, paracrine regulation specifically inhibits inflammatory cascades without causing excessive immune reprogramming, thereby maintaining delicate immune homeostasis in the wound microenvironment.

The *in vivo* mouse models of *S. aureus*-IDWs further corroborated the outstanding repair efficacy of the synergistic treatment. The ABC microneedle + US group achieved efficient bacterial clearance, accelerated re-epithelialization and collagen deposition, and significantly shortened the wound healing time within a 14-day observation period. Mechanistically, the combinatorial intervention restores cutaneous TRPV1/neuropeptide CGRP signaling, activates transcriptional programs related to vascular regeneration and neuroimmune regulation, and remodels the pathological transcriptomic landscape of IDWs toward a repair-oriented state. Doppler US imaging also verified the improved wound microcirculation, which provided sufficient nutritional support for subsequent tissue reconstruction.

Despite its promising therapeutic outcomes, this study has several limitations. First, the elevated CGRP signal in wound tissues cannot be strictly distinguished between exogenous microneedle release and endogenous neuronal synthesis; consequently, future genetic intervention experiments are required to clarify the causal relationship between CGRP signaling activation and wound repair. Second, *in vivo* vascular perfusion evaluation remains limited to qualitative observations and lacks quantitative indicators of vascular function. Third, the acute bacteria-infected diabetic wound mouse model used in this study cannot fully simulate the complex pathological characteristics of long-term chronic DWs seen in clinical patients. In addition, the

long-term biosafety and degradation behavior of Au-Bi₂S₃ composite microneedles still require systematic validation in large animal models.

This study therefore proposes an innovative, synergistic therapeutic strategy combining US-activated piezocatalytic microenvironment remodeling and protease-responsive neuroimmune regulation for infected DW repair. The engineered ABC microneedles simultaneously eliminate bacterial biofilm infection, correct the abnormal metabolic microenvironment of DWs, and restore CGRP-dependent neuroimmune homeostasis, thereby overcoming the therapeutic bottleneck of single anti-infection or neuroregulatory strategies. This study reveals the core regulatory role of neuroimmune crosstalk in infected diabetic wound healing and provides a feasible, safe, and multifunctional translational platform for the clinical treatment of refractory DFUs.

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Author contributions

Zhangqi Lai, Guo Zhang, Zhangyan, and Haijuan Teng contributed equally to this work. Zhangqi Lai, Guo Zhang, Jialong Chen, and Bangguo Zhou developed the idea, designed the experiment and contributed to the discussion and guidance of the article. Zhangqi Lai, Guo Zhang, Zhangyan, and Haijuan Teng carried out the in vitro and in vivo experiments. Zhangyan, Haijuan Teng, Miao Chen Wang, Jialong Chen, Bangguo Zhou participated in data collection, analysis and writ and revised manuscript.

Competing interests

The authors declare that they have no competing interests.

Ethics approval and consent to participate

All animal experiments were permitted by the Animal Care and Use Committee of Sichuan Provincial People's Hospital. All procedures were in accordance with the protocols permitted by the Animal Research Center of Sichuan Provincial People's Hospital.

Data Availability

The data supporting the results of this study can be obtained from the corresponding author upon reasonable request.

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