

RESEARCH ARTICLE

Neutrophil Extracellular Trap-Mimetic DNA Nets Enable Concurrent Bacteria-Targeted Eradication and Toxin Neutralization

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ABSTRACT

Current antibacterial therapies often suffer from limited bacterial selectivity, host-cell toxicity, and inflammation triggered by toxin release during bacterial killing. Here, we report a neutrophil extracellular traps (NETs)-mimetic, dopamine-incorporated DNA net, termed D^ANet-DA, enabling targeted bacterial eradication and concurrent toxin neutralization. Inspired by the trap-kill-neutralize function of NETs, D^ANet-DA selectively captures and traps bacteria, followed by in situ catalytic formation of polydopamine nanoshells on the trapped bacteria. This process enables efficient photothermal bacterial eradication while minimizing damage to host cells. Meanwhile, the nanoshells act as molecular sponges to sequester and neutralize bacterial toxins, thereby mitigating toxin-associated inflammation. These integrated functions endow D^ANet-DA with potent therapeutic efficacy in vivo, as demonstrated by markedly reduced bacterial burdens, toxin levels, tissue inflammation in both conventional and burn wound infection models. Moreover, the simultaneous clearance of bacteria and residual toxins alleviates pro-inflammatory macrophage polarization, thereby accelerating wound tissue regeneration. This work presents a NETs-mimetic antibacterial strategy that integrates pathogen clearance with toxin neutralization, offering a promising method for treating bacterial infection-associated diseases.

1 | Introduction

Bacterial infections rank among the leading causes of death worldwide, with an estimated 13.7 million infection-associated deaths annually, therefore remain a major threat to global health [1, 2]. They often disrupt host homeostasis and exacerbate systemic complications that causes death risk. Current clinical interventions still rely on systemic or topical antibiotic administration. However, the indiscriminate and excessive use of antibiotics has accelerated the emergence and dissemination of drug-resistant

bacteria, while also causing undesirable toxicity to host tissues [3]. Considerable efforts have been devoted to developing antibiotic-free alternatives, including antimicrobial peptides [4], charged polymers [5], artificial nanozymes [6], and bactericidal materials [7]. Although these emerging strategies have greatly expanded the antibacterial toolbox, most of them primarily focus on bacterial killing while overlooking the residual toxins released during bacterial lysis, which represent a critical yet underappreciated pathogenic issue. Bacterial toxins are generally classified according to their origin into lipid-derived endotoxins

Jun Li and Hao Yang contributed equally to this work.

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such as lipopolysaccharides and protein-based exotoxins such as enterotoxin [8, 9]. These toxins can trigger excessive host immune responses by activating nuclear factor NF- κ B signaling, resulting in persistent inflammation, amplified cytokine production, and impaired tissue regeneration [10–13]. Therefore, there is an urgent need for antibiotic-free therapeutic strategies that enable bacterial killing with concurrent toxin neutralization.

Nature offers an elegant antimicrobial solution through neutrophil extracellular traps (NETs), a sophisticated innate immune defense system that orchestrates bacterial entrapment, antimicrobial action, and toxin neutralization [14, 15]. Upon bacterial invasion, activated neutrophils are rapidly recruited to infected lesions and release NETs to eliminate pathogens through multiple cooperative mechanisms. First, the soft fibrous DNA networks, derived from decondensed nuclear chromatin, physically ensnare invading pathogens and confine them within localized antimicrobial microenvironments. Second, NETs-associated antimicrobial proteins, including neutrophil elastase, myeloperoxidase, and cathepsin G, eradicate captured bacteria through coordinated antimicrobial attacks [16]. Third, the DNA-rich networks can adsorb toxins released from lysed bacteria, contributing to toxin sequestration and neutralization in NETs [16–18]. Despite these attractive functions, the translation of natural NETs is fundamentally hindered by their highly variable and complex chemical compositions, potential pro-inflammatory risks, and the difficulty of reproducible biological extraction. Nevertheless, the distinctive trap-kill-neutralize mechanism of NETs provides a compelling nature-inspired framework for the design of antibacterial DNA biomaterials.

Herein, we report a biomimetic DNA-based platform, termed D^ANet-DA, which recapitulates the key structural and functional hallmarks of NETs for antibiotic-free treatment of bacterial infections and toxin-induced damage. D^ANet-DA integrates peptidoglycan-targeting aptamers (AptPGN), G4/hemin motifs, and dopamine (DA) substrates into a fibrous DNA net. We find that D^ANet-DA selectively captures bacteria and catalyzes in situ polydopamine (PDA) nanoshell formation, enabling precise photothermal bacterial eradication while preserving host cell viability. Critically, the PDA nanoshell further acts as a molecular sponge to sequester and neutralize the released bacterial toxins, attenuating toxin-driven inflammatory cascades. We demonstrate that D^ANet-DA achieves potent therapeutic efficacy in both conventional and burn wound infection models by simultaneously reducing bacterial burden, neutralizing toxins, suppressing NF- κ B-mediated inflammation, ultimately accelerating wound re-epithelialization. By addressing both microbial eradication and toxin neutralization within a single NETs-mimetic framework, this work offers a versatile, antibiotic-free strategy for the treatment of wound infections and other bacterial infection-associated diseases.

2 | Results and Discussion

2.1 | Design and Working Principle of D^ANet-DA

Inspired by the unique structural features of NETs, we design a multifunctional dopamine-incorporated DNA net (D^ANet-DA) for targeted antibacterial therapy through a coordinated trap-kill-

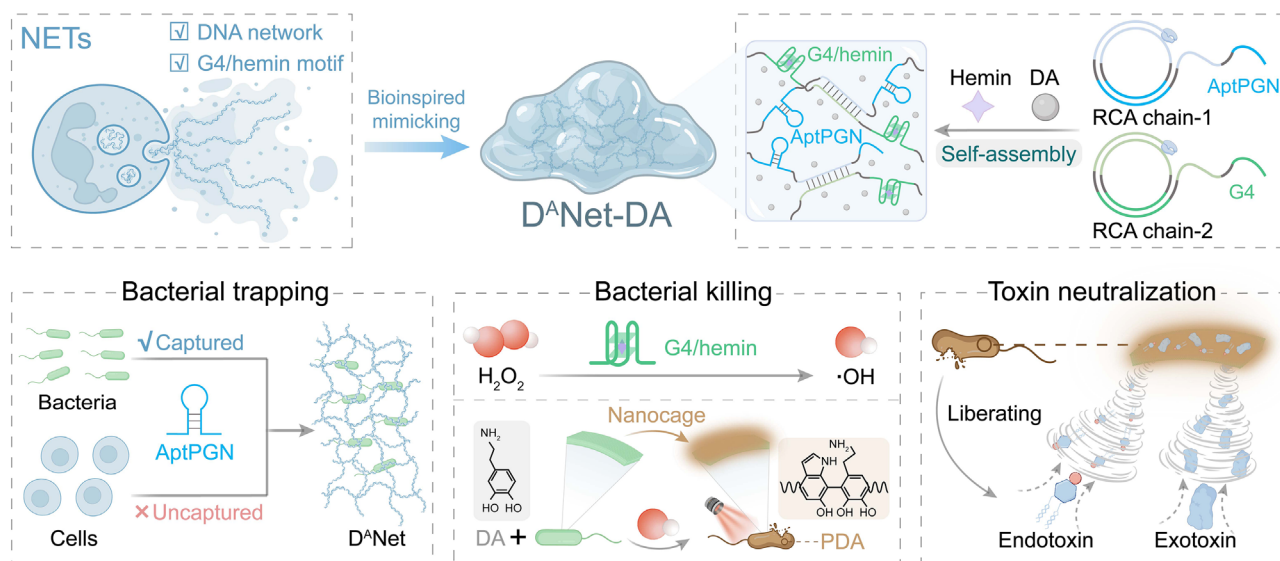
neutralize mechanism (Figure 1). The NETs-mimetic D^ANet-DA consists of three modules, poly-AptPGN sequences, peroxidase-mimicking poly-G4/hemin motifs, and DA substrates (Figure 1A). AptPGN endows D^ANet-DA with the ability to specifically recognize and capture bacteria. This bacteria-targeted recognition minimizes nonspecific interactions with host tissues, thereby improving the biocompatibility of D^ANet-DA. After bacterial capture, the NETs-like fibrous topology of D^ANet-DA further confines bacteria within the soft DNA network. Subsequently, in infected wound sites with elevated levels of H₂O₂ [19], the G4/hemin motifs catalyze endogenous H₂O₂ to generate ROS, which in turn immediately oxidize DA and trigger its localized polymerization into PDA. As a result, PDA nanoshells are formed in situ around the D^ANet-DA-trapped bacteria. These PDA nanoshells enable spatially confined photothermal killing of trapped bacteria under near-infrared (NIR) irradiation, and act as a molecular sponge to adsorb and neutralize toxins released upon bacterial lysis, such as lipopolysaccharide (LPS) and *Staphylococcus aureus* enterotoxin D (SED). Following this combined antibacterial and antitoxin treatment, proinflammatory M1 macrophage polarization and NF- κ B signaling are effectively suppressed, leading to reduced oxidative stress and attenuated inflammation in infected wounds (Figure 1B).

2.2 | Construction of D^ANet-DA

Guided by the above design, the DNA scaffold of D^ANet-DA, namely D^ANet, was synthesized via a one-pot rolling circle amplification (RCA). RCA generated single-strand DNA amplicons that self-assembled into a three-dimensional network (Figure 2A and Table S1). RCA chain-1 was designed to contain tandem repeat units composed of a AptPGN sequence [20] and a 20-nt segment complementary to RCA chain-2 for interstrand crosslinking, while RCA chain-2 additionally encoded repetitive G4-forming sequences.

We first characterized the formation, morphology, and structural features of D^ANet. As shown in Figure 2B, gel electrophoresis analysis showed that the circularized templates, Circ-1 and Circ-2, exhibited reduced electrophoretic mobility compared with their corresponding linear templates, Template-1 and Template-2, indicating successful circularization. The RCA products remained trapped in the loading wells owing to their large molecular weights, confirming the generation of extended RCA amplicons. After hybridization-mediated crosslinking between the two RCA amplicons, the resulting D^ANet was examined by cryo-scanning electron microscopy (cryo-SEM) and fluorescence microscopy (Figure 2C). Cryo-SEM images revealed a uniform reticulated porous morphology with pore sizes of ~10 μ m. Such a macroporous three-dimensional architecture is expected to facilitate bacterial infiltration into the DNA net, thereby favoring efficient bacterial ensnarement. Upon staining with the DNA-binding dye SYBR Green I, D^ANet exhibited homogeneous green fluorescence throughout the network (Figure S1). Rheological analysis showed that the storage modulus (G' , 7.8 Pa) was approximately 5.3 times higher than the loss modulus (G'' , 1.4 Pa) (Figure 2D), suggesting the formation of a soft hydrogel-like DNA net. This soft and compliant mechanical property may allow D^ANet to adapt to irregular wound surfaces.

A Design and construction of NETs-mimetic D^ANet-DA



B Antibacterial treatments enabled by D^ANet-DA

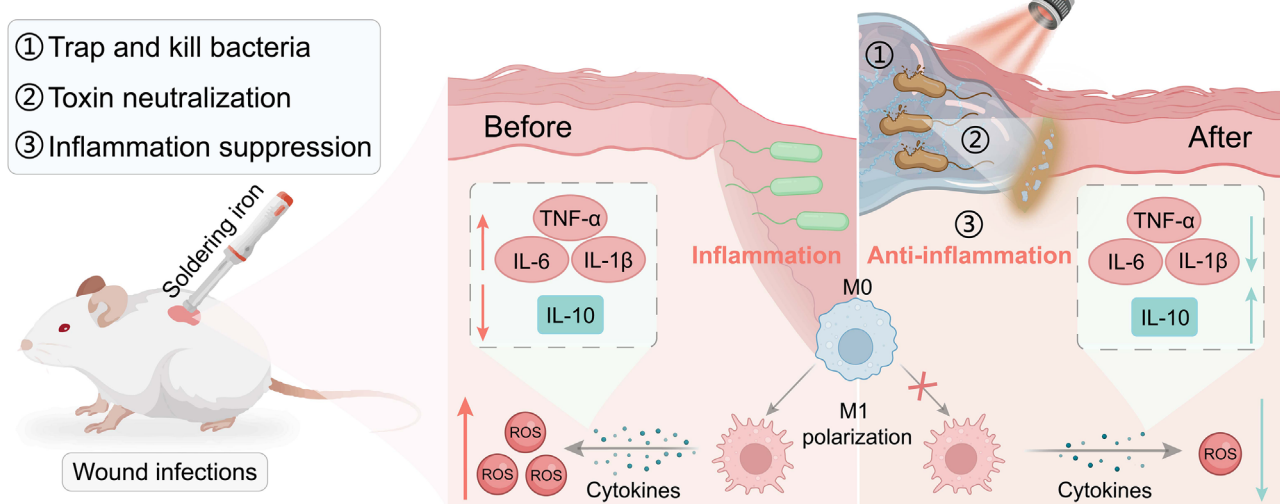


FIGURE 1 | Design and working principle of D^ANet-DA for antibacterial therapy and toxin neutralization. (A) D^ANet-DA is constructed by rolling circle amplification and self-assembly of peptidoglycan-targeting aptamers, G4/hemin catalytic motifs, and dopamine substrates. The resulting NETs-mimetic DNA net enables selective bacterial trapping, PDA nanoshell formation, localized photothermal bacterial killing, and toxin neutralization. (B) D^ANet-DA-mediated bacterial eradication and toxin neutralization suppress inflammatory responses, attenuate oxidative stress, modulate macrophage polarization, and accelerate wound healing.

We next verified the incorporation of AptPGN and G4/hemin motifs within the DNA net by x-ray photoelectron spectroscopy (XPS) and circular dichroism (CD) spectrum. The Fe signal detected by XPS confirmed the successful loading of hemin, an iron-containing porphyrin (Figure 2E), through its coordination with internal G4 structures in D^ANet. A monomeric repeat segment representing RCA chain-1, denoted Unit-1, exhibited a positive ellipticity signal at 190 nm that was consistent with that of synthetic AptPGN (Figure 2F), supporting the successful incorporation of the AptPGN motif into RCA chain-1. In addition, the CD spectra of a monomeric repeat segment representing RCA chain-2, denoted Unit-2, showed a red shift of the positive peak

from 275 nm to 270 nm upon addition of 140 mM K⁺ (Figure 2G), indicating the formation of G4 structures.

We further evaluated the peroxidase-like activity of D^ANet. G4/hemin complexes are known to catalyze H₂O₂-driven substrate oxidation via a hemin-centered iron-oxo intermediate [21]. A standard 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) colorimetric assay was performed to assess the catalytic activity of D^ANet. Compared with free G4 or free hemin, the G4/hemin complexes organized in D^ANet exhibited markedly enhanced catalytic performance as evidenced by the deeper green color of oxidized ABTS and the pronounced increase in the

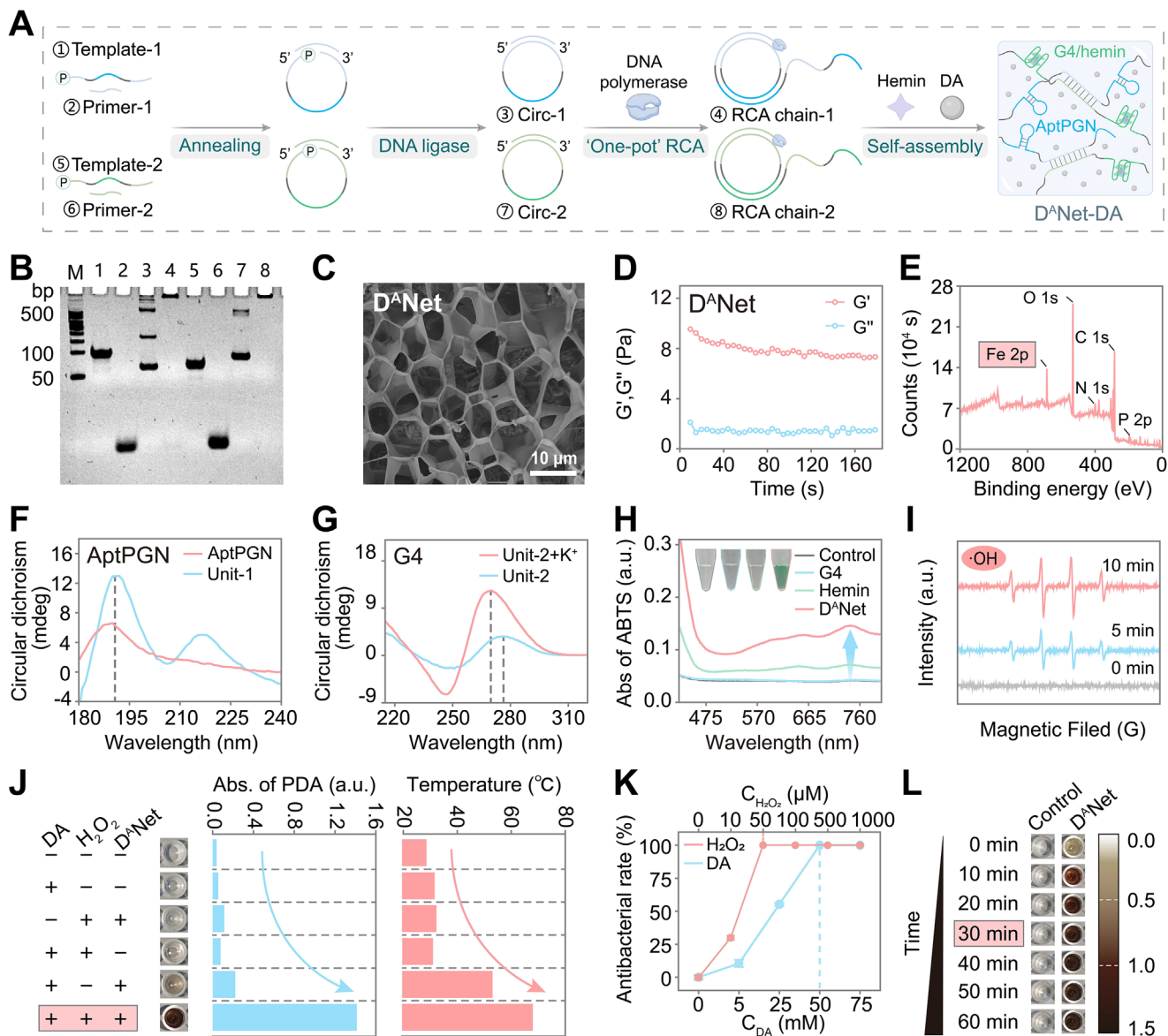


FIGURE 2 | Synthesis and characterization of D^ANet. (A) Schematic of the preparation process of D^ANet co-loaded with AptPGN and G4/hemin. (B) Polyacrylamide gel electrophoresis of primer-triggered RCA process. M: 50–500 bp marker; Lanes 1–8: Template-1, Primer-1, Circ-1, RCA chain-1, Template-2, Primer-2, Circ-2, and RCA chain-2. (C) Cryo-SEM morphology of D^ANet. (D) Rheological tests of D^ANet. (E) XPS spectrum of D^ANet. (F) CD spectra of a synthetic AptPGN and a monomeric repeat segment (Unit-1) representing RCA chain-1. (G) CD spectra of a monomeric repeat segment (Unit-2) representing RCA chain-2 with or without 140 mM K⁺. (H) The peroxidase-like activity of control, G4 alone, hemin alone, and D^ANet groups as determined by ABTS assay. (I) ESR spectrum of ·OH radicals catalytically generated by D^ANet. (J) The dependence of PDA formation on DA, H₂O₂, and D^ANet, and the photothermal performance of PDA products. (K) Optimization of H₂O₂ and DA concentration based on antibacterial plate assays ($n = 3$, mean $\pm$ SD). (L) Determination of the optimal reaction time for PDA formation catalyzed by D^ANet.

characteristic absorbance of ABTS^{·+} at 405 and 734 nm (Figure 2H). To identify the radical species generated during catalysis, electron spin resonance (ESR) spectroscopy was performed. The ESR results confirmed that D^ANet activated H₂O₂ to produce hydroxyl radicals (·OH) (Figure 2I), which can further drive downstream oxidation reactions, including DA polymerization.

Given the strong oxidizing capacity of ·OH radicals, we next examined whether D^ANet could drive the oxidative polymerization of DA into PDA. Under the tested conditions, DA showed negligible self-polymerization, whereas the coexistence of D^ANet and H₂O₂ efficiently initiated PDA formation (Figures 2J and

S2). The resulting PDA exhibited pronounced photothermal performance upon 808 nm NIR irradiation. To further improve catalytic performance, we optimized the critical reaction conditions, with all reactions conducted in an H₂O₂-rich, mildly acidic, biocompatible HEPES buffer that simulates the in vivo wound microenvironment [22]. Before DA polymerization assays, the hemin loading was optimized and reached a plateau at 40 μM hemin (Figure S3). Antibacterial plate assays showed that the antibacterial efficiency rose progressively with increasing DA and H₂O₂ concentrations, reaching nearly 100% at 50 mM DA and 50 μM H₂O₂ (Figures 2K, S4, and S5). We subsequently monitored the kinetics of D^ANet-catalyzed PDA formation. The

UV-vis absorption of PDA gradually increased over the catalytic reaction period and became pronounced at 30 min, with only minimal change thereafter (Figures 2L and S6), suggesting that PDA formation was nearly complete within 30 min. To optimize NIR irradiation time for PDA-mediated photothermal treatment, antibacterial efficacy was evaluated at different irradiation times, with 4 min achieving nearly complete bacterial eradication, while reaching a macroscopic temperature of approximately 47°C (Figure S7).

The reproducibility and long-term storage stability of D^ANet were assessed based on its morphological integrity and antibacterial activity. Independently prepared batches exhibited consistent Cryo-SEM and macroscopic morphologies, indicating robust batch-to-batch reproducibility (Figure S8). Moreover, D^ANet retained its characteristic morphology after 21 days of storage at room temperature and, upon subsequent incubation with DA, yielded D^ANet-DA with pronounced antibacterial efficacy, demonstrating favorable storage stability and retention of antibacterial functionality (Figure S9). Collectively, these results verify the successful construction of the NETs-mimetic DNA net and validate its structural features and key functional properties underlying its antibacterial design.

2.3 | D^ANet-DA Selectively Eradicates Bacteria via a Trap-and-Kill Mechanism

We evaluated the bacterial selectivity and antibacterial potency of D^ANet-DA, and investigated the trap-and-kill mechanism. Leveraging the bacteria-specific binding affinity of AptPGN, the designed DNA net is expected to selectively trap bacteria while minimizing interactions with host cells. *Escherichia coli* (*E. coli*) is selected as the representative challenging model strain for subsequent antibacterial evaluation, as its lower peptidoglycan content renders Gram-negative bacteria less susceptible to AptPGN recognition than Gram-positive bacteria [23].

To characterize the bacterial trapping capability of the biomimetic DNA net, Cy5-labeled D^ANet or DNet lacking AptPGN was incubated with green fluorescent protein (GFP)-expressing *E. coli*, followed by fluorescence co-localization imaging. Robust *E. coli* GFP signals were evident throughout the AptPGN-containing D^ANet (Figure 3A, top), whereas negligible bacterial fluorescence was detected in the AptPGN-free DNet (Figure 3A, bottom), highlighting the indispensable role of AptPGN in bacterial capture. Furthermore, we examined whether AptPGN prebinding affects subsequent D^ANet-mediated capture of *E. coli* using FAM-AptPGN and Cy5-D^ANet (Figure S10). Following incubation with FAM-AptPGN, strong FAM fluorescence was observed across the bacterial surface, confirming efficient binding of AptPGN to *E. coli*. Notably, these FAM-AptPGN-prebound bacteria were not observed within the Cy5-labeled D^ANet network after subsequent incubation with Cy5-D^ANet, indicating that pre-occupation of the bacterial surface by AptPGN prevents subsequent D^ANet-mediated capture. These results provide direct evidence that DNet-mediated bacterial ensnarement relies on AptPGN-dependent recognition. The observed bacterial entrapment can be attributed to the ~10 µm pores of D^ANet being sufficiently large to permit penetration of *E. coli* (1–5 µm in length), while the AptPGN-functionalized DNA

scaffold subsequently retains the infiltrated bacteria within the network.

The binding selectivity of AptPGN was preliminarily evaluated by incubating Cy5-labeled AptPGN with *E. coli*, methicillin-resistant *Staphylococcus aureus* (MRSA), or L929 fibroblasts. Cy5-AptPGN shows strong binding to both *E. coli* and MRSA but minimal association with L929 cells (Figure S11), supporting its preferential recognition of bacteria over mammalian cells. Then, a bacteria-mammalian cell co-incubation system was further established to assess the bacterial selectivity of D^ANet under a more complex biological setting. Briefly, Cy5-labeled D^ANet was added to tubes containing a mixed suspension of GFP-*E. coli* and DAPI-stained RAW264.7 macrophage cells, followed by incubation at 37°C for 1 h. After being gently washed with PBS, the samples were imaged by confocal microscopy, with the mixture before D^ANet-mediated capture as the control. D^ANet selectively captured and trapped bacteria, while showing negligible association with co-cultured mammalian cells (Figure 3B). These results demonstrate the preferential bacterial affinity of D^ANet and its minimal nonspecific interaction with host cells.

We proceeded to explore whether D^ANet-DA could effectively kill the trapped bacteria by PDA-mediated photothermal effects. Before photothermal antibacterial evaluation, the PDA encapsulation behavior on bacteria was examined by transmission electron microscope (TEM) characterization and fluorescence co-localization imaging. TEM images revealed an electron-dense thin layer tightly surrounding bacterial cells after D^ANet-DA treatment, suggesting the generation of a surface coating on bacteria (Figure 3C). Using GFP-*E. coli* together with a Cy5-NHS probe selective for PDA labeling (Figure S12), fluorescence co-localization analysis further verified the PDA nature of this coating, confirming the formation of well-defined PDA nanoshells around bacteria. The average thickness of the PDA nanoshell is approximately 182 ± 2 nm (Figures 3D and S13).

We hypothesized that D^ANet-DA would exhibit potent antibacterial activity due to the strong photothermal effect of PDA nanoshells. As a proof of concept, drug-sensitive *E. coli* and MRSA isolated from clinical specimens were selected as representative bacterial strains for the test. Different formulations, including PBS, DA, D^ANet, DNet-DA, D^ANet-DA were incubated with bacteria for 30 min, and then exposed to NIR laser irradiation for 10 min. The antibacterial efficacy was first assessed by LIVE/DEAD fluorescent staining (Figure 3E). DA alone showed no detectable antibacterial effect. Compared with DA group, D^ANet treatment induced a slight increase in dead bacteria-derived red fluorescence in both *E. coli* and MRSA, suggesting moderate bactericidal activity that may arise from G4/hemin-induced oxidative damage. In contrast, both DNet-DA and D^ANet-DA exhibited pronounced bactericidal effects, with D^ANet-DA showing the strongest antibacterial performance.

SEM further confirmed the antibacterial damage induced by D^ANet-DA. Compared with other groups, *E. coli* and MRSA treated with D^ANet-DA displayed the most severe morphological disruption, including cell deformation, surface collapse, and membrane rupture (Figures 3E and S14). The antibacterial efficiency of each group was further quantitatively evaluated using a standard colony-forming unit (CFU) assay (Figures 3F

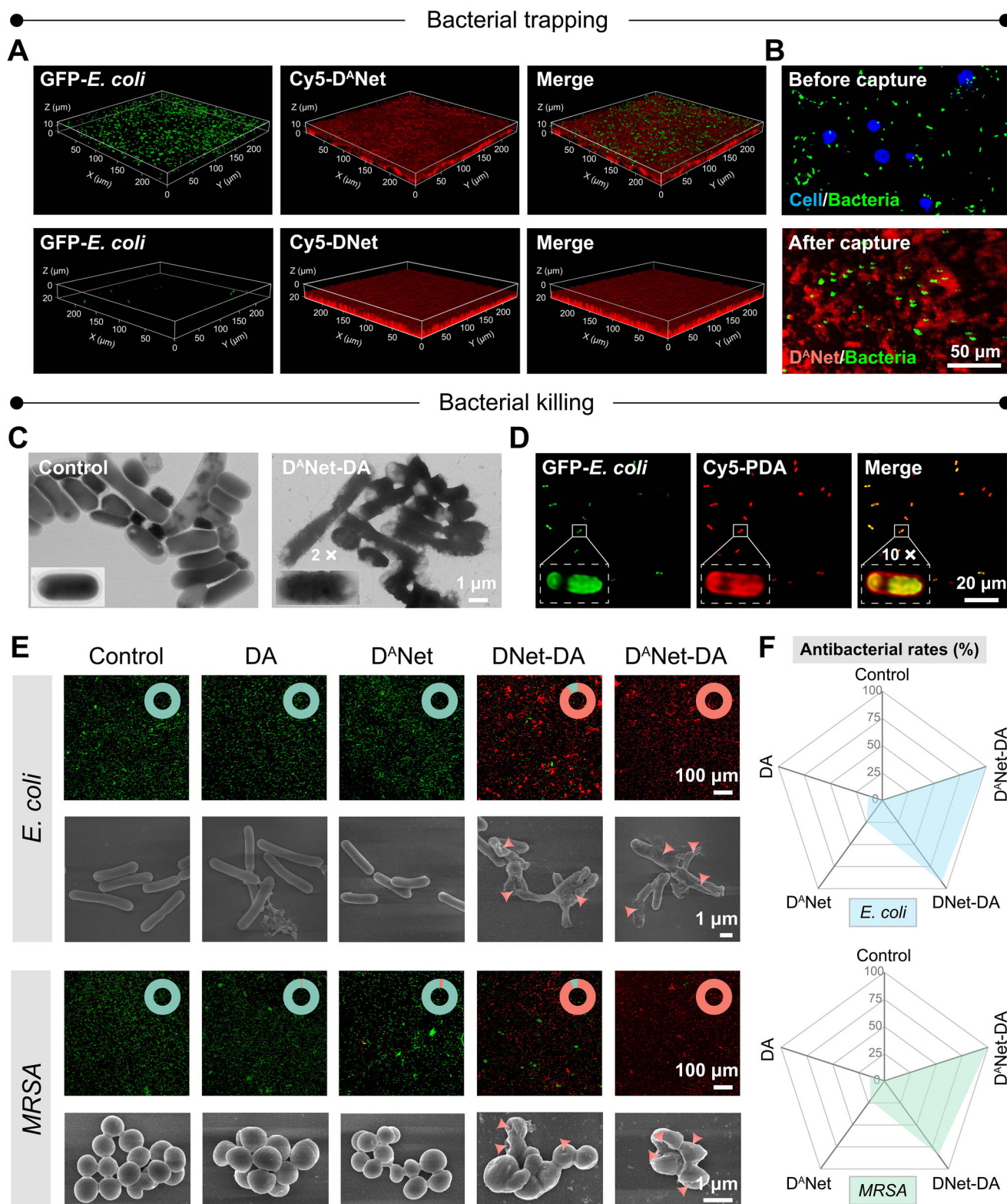


FIGURE 3 | In vitro assessment of D^ANet-mediated bacterial trapping and killing performance against *Escherichia coli* and methicillin-resistant *Staphylococcus aureus* (MRSA). (A) Confocal microscopy 3D imaging of GFP-*E. coli* captured within Cy5-labeled D^ANet and DNet networks. (B) Confocal fluorescence imaging of the selective capture of GFP-*E. coli* by Cy5-labeled D^ANet over DAPI-stained mammalian RAW264.7 cells. (C) TEM images of *E. coli* in control and D^ANet-DA groups. (D) Fluorescence co-localization imaging of Cy5-modified PDA nanoshell around D^ANet-trapped GFP-*E. coli*. (E) Live/Dead fluorescent and SEM images of *E. coli* and MRSA treated with PBS, DA, D^ANet, DNet-DA and D^ANet-DA upon NIR irradiation. The red arrows indicate the ruptures of bacteria. (F) Antibacterial rates of *E. coli* and MRSA treated with PBS, DA, D^ANet, DNet-DA, and D^ANet-DA upon NIR irradiation.

and S15). Consistent with the fluorescence and SEM results, DNet-DA exhibited strong bactericidal activity, achieving killing efficiencies of $92.42 \pm 0.93\%$ against *E. coli* and $84.13 \pm 2.37\%$ against MRSA. Notably, no visible colonies of either *E. coli* or MRSA were observed after D^ANet-DA treatment, indicating near-complete bacterial eradication. These results demonstrate that D^ANet-DA enables targeted capture and trapping of bacteria, and subsequently eradicates the trapped bacteria through localized PDA-mediated photothermal action.

2.4 | D^ANet-DA Sequesters Residual Bacterial Toxins via Multivalent Interactions

We next investigated whether D^ANet-DA could sequester residual bacterial toxins. Considering the broad molecular adsorption capability of PDA nanoshells (Figure 4A), we tested the depletion of different toxins and chose LPS, a major endotoxin component, and SED, a representative exotoxin, for the test. Bacterial samples pretreated with PBS as the control, DA, D^ANet, pre-formed PDA or D^ANet-DA were incubated with fluorescein isothiocyanate (FITC)-labeled LPS and unlabeled SED. After incubation and centrifugation, the residual FITC-LPS and SED levels in the supernatant were quantified using fluorometric analysis and enzyme-linked immunosorbent assay (ELISA), respectively. As shown in Figure 4B,C, DA and D^ANet alone exhibit minimal antitoxin activity, with no significant difference from the control group. In contrast, D^ANet-DA markedly reduced the residual levels of both LPS and SED, demonstrating its pronounced toxin-sequestering capability. Notably, pre-formed PDA showed comparable adsorption of both toxins to D^ANet-DA, confirming that this capacity primarily arises from the intrinsic adsorption property of the PDA nanoshell rather than the DNA scaffold.

To elucidate the mechanism by which PDA captures LPS and SED, we performed molecular docking and dynamics simulations. In the docking analysis, a representative PDA monomer was modeled as the ligand, while LPS or SED was used as the receptor. The docking results provide an illustrative view of the potential interactions between PDA and LPS or SED (Figure 4D,E), offering preliminary structural insights into their possible binding modes. To further verify the docking-derived interactions under physiological states, all-atom molecular dynamics simulations were conducted. A PDA layer was constructed by assembling PDA decamers into an approximately 12×12 nm plane interface, and model LPS and SED molecules were initially placed approximately 1.6 and 2.0 nm above the PDA interface, respectively. After a 20 ns equilibration period, the interaction between PDA and LPS or SED was monitored over 500 ns. Root mean square deviation (RMSD) analysis showed that both PDA-LPS and PDA-SED interactions reached equilibrium at approximately 100 ns, and maintained stable structural parameters thereafter, indicating a stable binding conformation (Figure S16). Representative side-view snapshots at 0, 10, 50, 100 and 500 ns, together with enlarged views of the LPS or SED configurations on the PDA layer at 500 ns were taken to visualize the evolution of interfacial configurations (Figure 4F,G). The sequential snapshots revealed that both toxins gradually approached and became firmly adsorbed onto the PDA interface during the simulation.

The interaction patterns were further quantified by calculating the average number of contacts during the simulation. PDA-LPS binding is mainly mediated by hydrogen-bonding (~ 2 contacts) and hydrophobic interactions (~ 10 contacts) (Figures 4H and S17A). In contrast, PDA-SED involved a broader interaction network, comprising approximately seven hydrogen-bonding contacts, one hydrophobic interactions contact, one cation- π interaction, and one π - π stacking interaction (Figures 4I and S17B). Owing to the well-defined amino acid sequence and tertiary structure of SED, residue-resolved interaction analysis was further performed for the PDA-SED system (Figures S18 and S19). This analysis reveals that the PDA-SED interface is dominated by hydrogen bonding and hydrophobic interactions across most binding sites, whereas cation- π interactions are selectively enriched at Lys residues such as Lys227 and Lys39. By comparison, π - π stacking is relatively limited and was mainly observed around His38. These distinct interaction profiles can be attributed to the different structural features of the two toxins. The ordered protein structure of SED exposes diverse aromatic and cationic residues, enabling defined and cooperative interactions with PDA, including residue-specific cation- π and π - π stacking. Unlike SED, LPS lacks abundant aromatic moieties for specific interfacial recognition, and therefore interacts with PDA mainly through broadly distributed and nonspecific hydrogen-bonding and hydrophobic interactions. Overall, these multivalent PDA-toxin interactions provide molecular-level insights into the potential mechanisms underlying the toxin-sequestering and neutralizing activity of D^ANet-DA.

2.5 | Neutralization of Toxins Alleviates Inflammatory Responses

We then evaluated whether the toxin-neutralizing activity of D^ANet-DA could alleviate the toxin-driven inflammatory responses in immune cells. The cytocompatibility of D^ANet-DA was first examined using L929 fibroblasts via a CCK-8 assay (Figure S20). The cell viability observed in the D^ANet-DA group was comparable to that of the control group, confirming the favorable cytocompatibility of D^ANet-DA. The cellular response to the complete photothermal treatment was further evaluated by live/dead staining after D^ANet-DA treatment followed by NIR irradiation. Confocal imaging revealed negligible cell death compared with the control group (Figure S21), indicating minimal cytotoxicity of 4-min NIR irradiation in the presence of D^ANet-DA. This favorable biocompatibility is likely attributable to the short duration of NIR exposure, together with the intrinsic biocompatibility of the DNA scaffold and PDA.

Toxins released after bacterial eradication are known to trigger robust inflammatory activation in immune cells [24, 25]. Given that macrophages serve as frontline responders in the immune defense [26, 27], RAW264.7 mouse macrophage cell was selected as the cellular model to investigate the inflammatory responses induced by LPS and SED, as well as the toxin-neutralizing effect of D^ANet-DA. Whole-transcriptome RNA sequencing was performed to elucidate the intracellular mechanism underlying D^ANet-DA-mediated toxin sequestration. Principal component analysis showed clear separation between the toxin model groups (LPS and SED), and the corresponding D^ANet-DA treatment groups (LPS+D^ANet-DA and SED+D^ANet-DA). Biological

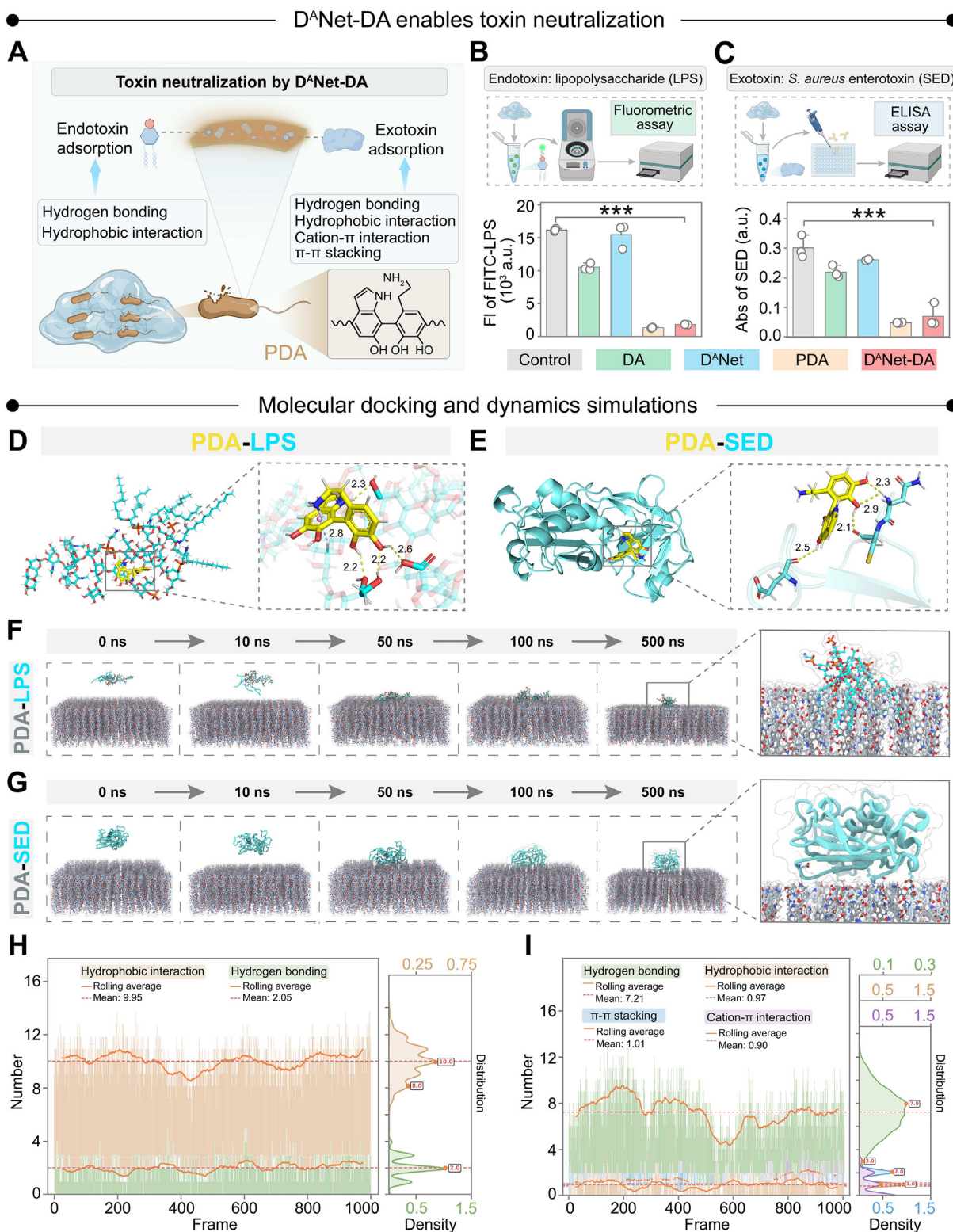


FIGURE 4 | Assessment of toxin neutralization effect and mechanism of D^ANet-DA. (A) Schematic illustration of mechanism by which D^ANet-DA mediates toxin adsorption. (B) Fluorescence of FITC-LPS following treatment with PBS (Control), DA, D^ANet, pre-formed PDA, and D^ANet-DA ($n = 3$, mean $\pm$ SD). (C) Absorbance measurements obtained from enzyme-linked immunosorbent assay (ELISA) to quantify SED following treatment with PBS (Control), DA, D^ANet, pre-formed PDA and D^ANet-DA ($n = 3$, mean $\pm$ SD). Computational analysis of PDA oligomer secondary structure and docking interactions with (D) LPS and (E) SED. Representative snapshots and enlarged views depicting the interaction of (F) LPS and (G) SED with a PDA layer. (H) Contact numbers of different interactions during the PDA-LPS binding process, including hydrophobic interaction and hydrogen bonding. (I) Contact numbers of different interactions during the PDA-SED binding process, including hydrogen bonding, hydrophobic interaction, π - π stacking, and cation- π interaction. Statistical differences (p -values) are evaluated by one-way ANOVA with Tukey's multiple-comparisons test in B and C. *** represents $p < 0.001$.

replicates within each group clustered tightly, indicating good reproducibility and distinct transcriptional responses among groups (Figure 5A). D^ANet-DA treatment markedly reshaped toxin-induced inflammatory transcriptional profiles. In the LPS model, 5287 differentially expressed genes (DEGs) were identified in LPS+D^ANet-DA versus LPS, including 2790 downregulated and 2497 upregulated genes (Figure 5B). In the SED model, 1683 DEGs were identified in SED+D^ANet-DA versus SED, including 891 downregulated and 792 upregulated genes (Figure 5C). Hierarchical clustering analysis of the top 20 key DEGs revealed marked distinct clustering between D^ANet-DA-treated and toxin-stimulated macrophages, involving several inflammation-associated genes, such as *Acod1* [28], *Akt2* [29], and *Ccl4* [30] (Figure S22), thereby indicating substantial transcriptional remodeling after D^ANet-DA treatment.

Gene Ontology (GO) enrichment analysis of LPS+D^ANet-DA versus LPS highlighted the biological process terms closely related to inflammatory and innate immune programs [31], including “regulation of inflammatory response,” “response to lipopolysaccharide,” and “regulation of cytokine production” (Figure 5D). A similar enrichment pattern was observed in the SED model, in which D^ANet-DA treatment modulated the inflammatory and innate immune processes, including “regulation of interleukin-6 production,” “activation of innate immune response,” and “regulation of cytokine production” (Figure 5G). Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway analysis further indicated that D^ANet-DA broadly affected inflammation-associated signaling cascades with notable enrichment in NF- κ B, TNF and Toll-like receptor signaling pathways in both the LPS and SED models (Figure 5E,H). Gene set enrichment analysis (GSEA) further revealed negative enrichment trends for NF- κ B, TNF, and Toll-like receptor signaling pathways in D^ANet-DA-treated groups compared with the corresponding toxin model groups (Figure 5F–I). These transcriptomic results suggest that bacterial toxins activate pro-inflammatory signaling in macrophages, whereas D^ANet-DA attenuates these responses by neutralizing toxins and suppressing inflammatory pathway activation.

We further examined the regulatory effect of D^ANet-DA on NF- κ B signaling activation. Canonical NF- κ B, an active DNA-binding dimer composed of p50 and p65, is widely used as a marker of inflammatory pathway activation [32, 33]. In the inactive state, NF- κ B forms a complex with I κ B in the cytoplasm of macrophages. Upon stimulation by inflammatory signals such as LPS or SED, I κ B is phosphorylated and degraded, leading to NF- κ B activation and the transcription of pro-inflammatory genes. To quantitatively evaluate the NF- κ B signaling activation, western blot analysis was conducted to determine the phosphorylation levels of key regulatory proteins, including p65 and I κ B α (Figure 6A,B). The results show that stimulation with either LPS or SED markedly elevates the phosphorylation levels of p65 and I κ B α , whereas D^ANet-DA treatment significantly attenuated their phosphorylation, restoring them to levels comparable to those in untreated controls. These results indicate that D^ANet-DA effectively inhibits toxin-induced NF- κ B pathway activation in macrophages.

We then evaluated the inflammatory responses of RAW264.7 cells by quantifying the mRNA levels of key proinflammatory cytokines including tumor necrosis factor- α (TNF- α), interleukin-

1 β (IL-1 β), and interleukin-6 (IL-6), using reverse transcription quantitative real-time PCR (RT-qPCR). As shown in Figures 6C and S23, stimulation with either LPS or SED markedly upregulated all three cytokines. Specifically, compared with the untreated group, LPS stimulation increased the mRNA levels of TNF- α , IL-1 β , and IL-6 by approximately 12.1-, 15.7-, and 10.7-fold, respectively, whereas SED stimulation increased them by 5.0-, 7.5-, and 4.7-fold, respectively. After D^ANet-DA treatment, the expression levels of these pro-inflammatory cytokines were significantly reduced and approached those of the control group. Such variation in pro-inflammatory cytokine expression may be associated with changes in immunostimulatory cell populations, such as M1 macrophages [34]. Therefore, we next evaluated the effect of toxin neutralization on macrophage polarization. LPS and SED were pretreated with D^ANet-DA, followed by centrifugation and collection of the supernatants for incubation with RAW264.7 macrophages. Flow cytometric analysis of CD80 and CD206 expression showed that LPS or SED stimulation increased the proportion of CD80⁺ macrophages, whereas D^ANet-DA treatment resulted in CD80⁺ population comparable to those of the untreated control (Figure 6D). CD206 expression showed no pronounced changes among the different treatments, indicating no marked effect on M2 polarization. These findings indicate that D^ANet-DA-mediated toxin neutralization effectively suppresses LPS- and SED-induced inflammatory responses and M1 macrophage polarization.

The anti-inflammatory effect of D^ANet-DA was further validated by monitoring intracellular ROS levels in macrophages. Intracellular ROS contents were measured using the ROS-sensitive fluorescent probe, 2',7'-dichlorofluorescein diacetate (DCFH-DA). As shown in Figure 6E, challenge with either LPS or SED markedly increases intracellular ROS levels, as reflected by the strong DCFH-DA fluorescence observed in the treated cells. Given the potential pro-inflammatory effects of pathological NETs [35], we therefore assessed the intrinsic inflammatory potential of D^ANet-DA and found that D^ANet-DA alone did not induce appreciable DCFH-DA fluorescence in macrophages. In contrast, the D^ANet-DA-treated cells exhibit markedly reduced fluorescence signals, with ROS levels comparable to those of untreated controls. These results indicate that, D^ANet-DA efficiently suppresses toxin-induced oxidative stress in macrophages by neutralizing LPS and SED. Taken together, these results demonstrate that D^ANet-DA alleviates toxin-induced macrophage inflammation by sequestering bacterial toxins, inhibiting NF- κ B pathway activation, reducing pro-inflammatory cytokine expression, and suppressing intracellular oxidative stress (Figure 6F). Through the combined bacterial clearance and toxin-associated inflammatory resolution, the NETs-mimetic DNA net provides a promising therapeutic strategy for promoting infected wound healing.

2.6 | D^ANet-DA Accelerates Healing of Infected Wounds

Prior to in vivo evaluation, the stability of the DNA net under infection-relevant conditions was investigated. D^ANet was incubated at 37°C in simulated infected wound fluid containing 10% FBS and the supernatant of an *E. coli* culture (10⁸ CFU/mL). D^ANet remained morphologically stable with minimal DNA degradation for up to 4 h, with gradual degradation observed

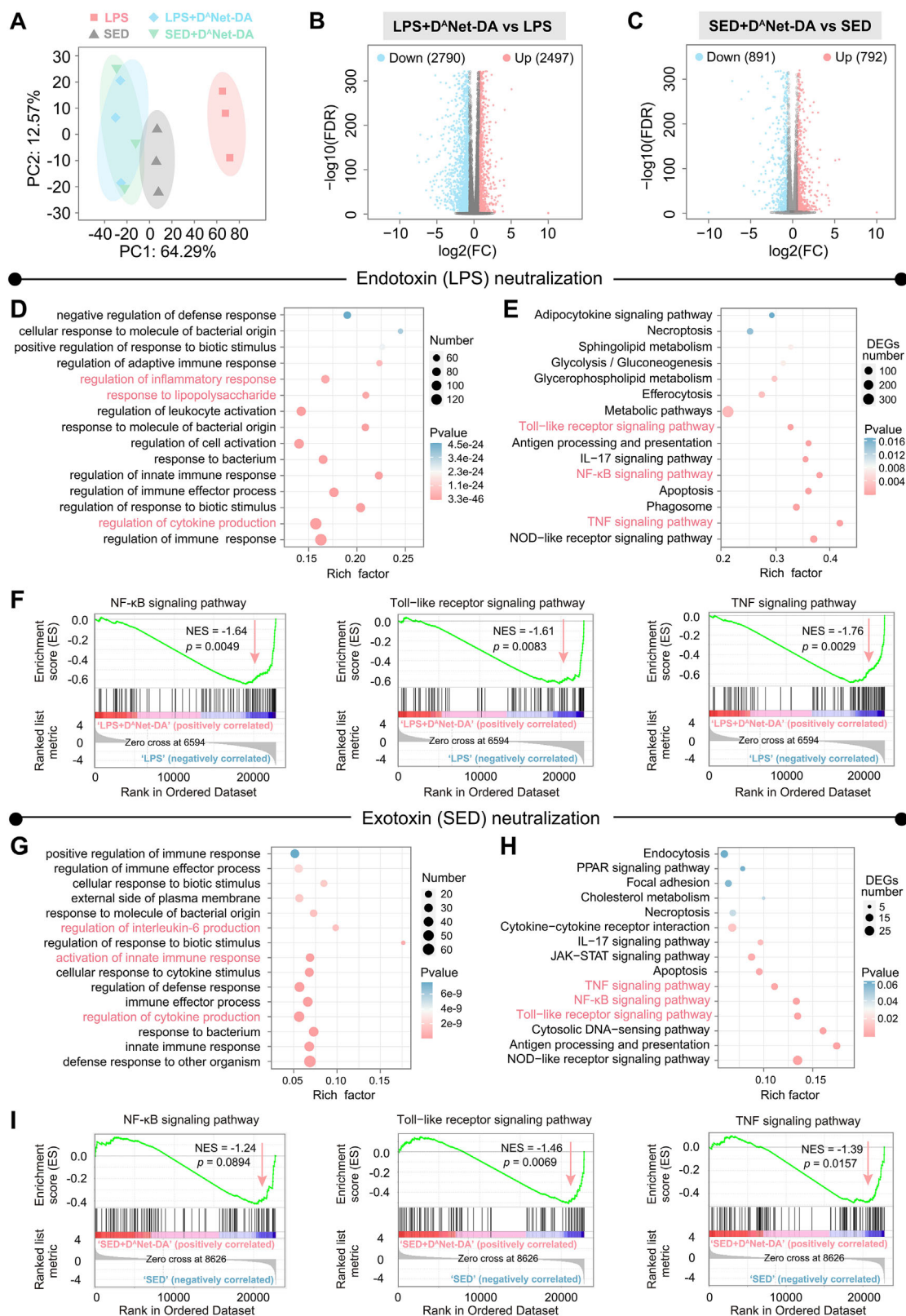


FIGURE 5 | Transcriptomic analysis of the antitoxin mechanism. (A) Principal component analysis of whole-transcriptome RNA sequencing data from different groups (LPS, SED, LPS+D^ANet-DA, and SED+D^ANet-DA). Volcano plots of DEGs for (B) LPS+D^ANet-DA versus LPS and (C) SED+D^ANet-DA versus SED. (D) GO annotation results of DEGs for LPS+D^ANet-DA versus LPS. (E) KEGG pathway enrichment analysis of DEGs for LPS+D^ANet-DA versus LPS. (F) GSEA for inflammatory signaling pathway with respect to endotoxin neutralization. (G) GO annotation results of DEGs for SED+D^ANet-DA versus SED. (H) KEGG pathway enrichment analysis of DEGs for SED+D^ANet-DA versus SED. (I) GSEA analysis of inflammatory signaling pathway involving exotoxin neutralization. Three independent biological replicates were analyzed for each group ($n = 3$).

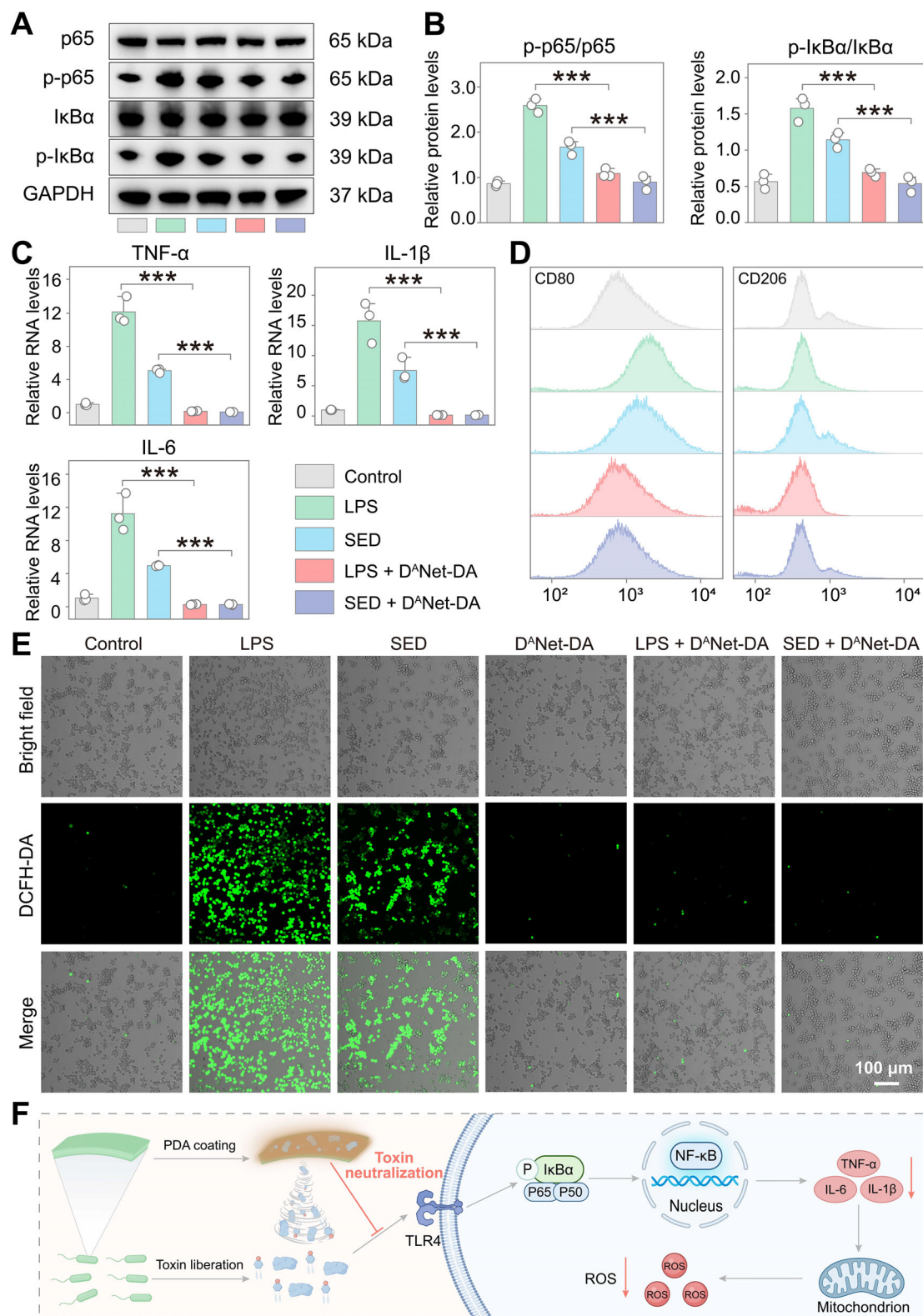


FIGURE 6 | Validation of anti-inflammatory effects of D^ANet-DA in bacterial toxin-stimulated RAW264.7 cells. (A) Western Blot analysis and (B) corresponding quantitative evaluation of the phosphorylation levels of key proteins (p-p65/p65 and p-IκBα/IκBα) involved in the NF-κB pathway after 24 h of various treatments ($n = 3$, mean $\pm$ SD). (C) RT-qPCR quantification of TNF-α, IL-1β, and IL-6 mRNA levels in RAW264.7 cells following 24 h exposure to various materials ($n = 3$, mean $\pm$ SD). (D) Flow cytometric analysis of CD80⁺ and CD206⁺ RAW264.7 macrophages following 24 h exposure to different treatments. (E) Representative fluorescence images of intracellular ROS in RAW264.7 cells following 24 h treatments using ROS-specific DCFH-DA probe ($n = 3$, mean $\pm$ SD). (F) Schematic illustration of mechanism by which D^ANet-DA neutralizes toxins and modulates anti-inflammatory pathways. Statistical differences (p -values) are evaluated by one-way ANOVA with Tukey's multiple-comparisons test in B and C. *** represents $p < 0.001$.

thereafter (Figure S24). This stability is sufficient to maintain D^ANet integrity throughout the 0.5 h therapeutic period (Figure S25). Following the treatment procedure, extensive PBS debridement physically removed the DNA net, trapped bacteria, and associated PDA nanoshells, while residual DNA progressively degraded into smaller nucleic acid fragments that can undergo physiological processing and clearance. PDA has been reported to exhibit favorable in vivo biocompatibility without apparent histopathological toxicity after prolonged tissue exposure [36], suggesting that the residual D^ANet-DA components are unlikely to adversely affect wound healing.

The in vivo applicability of D^ANet-DA was first evaluated in a simple *E. coli*-infected wound model representing Gram-negative wound infection, where D^ANet-DA administration markedly reduced the bacterial burden and residual *E. coli*-derived LPS level (Figures S26 and S27). These findings provide preliminary evidence for the dual antibacterial and toxin-neutralizing activities of D^ANet-DA. Given the clinical relevance and therapeutic challenges associated with *MRSA* as a Gram-positive and multidrug-resistant wound pathogen, subsequent comprehensive in vivo evaluations focus on *MRSA*.

For the *MRSA* challenge, we first established a conventional wound model by inoculating female Kunming mice with clinically isolated *MRSA* strains (Figure 7A). The wound healing process was monitored over 10 days. On day 1 after treatment, residual bacteria in wound exudates were collected using sterile swabs and quantified by CFU assay. D^ANet-DA treatment achieved near-complete bacterial eradication, whereas a higher level of bacterial survival remained in the DNet-DA group, with an antibacterial rate of $64.2 \pm 2.9\%$, highlighting the potent antibacterial efficacy of D^ANet-DA (Figures 7D and S28). During the treatment period, D^ANet-DA group exhibited markedly accelerated wound closure compared with the other groups from day 4 onward, as evidenced by the rapid reduction in wound traces over subsequent days (Figure 7B). On day 10, wounds treated with DNet-DA and D^ANet-DA showed substantial contraction, with the final wound healing rate increasing to around $77.9 \pm 10.1\%$ and $95.2 \pm 3.0\%$, respectively (Figure 7C). In contrast, D^ANet, which lacks the DA component, induced only partial wound closure, indicating the indispensable role of PDA-mediated antibacterial and antitoxin actions in achieving therapeutic efficacy. Notably, the superior antibacterial and wound-healing efficacy of D^ANet-DA compared with DNet-DA further underscore the pivotal contribution of AptPGN-mediated bacterial targeting, which facilitates localized bacterial capture and enhances subsequent bactericidal activity.

To gain deeper insights into the wound healing process, skin tissues surrounding the wound sites were harvested from each group on day 10. The tissues were subjected to hematoxylin-eosin (H&E) staining for histological analysis, as well as immunofluorescent staining for interleukin-6 (IL-6), a typical pro-inflammatory cytokine [37, 38] and interleukin-10 (IL-10), a typical anti-inflammatory cytokine [39]. H&E staining showed that D^ANet-DA markedly accelerated the wound contraction, as characterized by more complete epidermal regeneration and the greatest granulation tissue thickness among all groups (Figures 7E (top) and S29). Immunofluorescent imaging further revealed that wounds treated with D^ANet-DA exhibited the lowest IL-6 expres-

sion and the highest IL-10 expression (Figure 7E(bottom),F), indicating that D^ANet-DA effectively attenuates local inflammation and promotes the establishment of an anti-inflammatory microenvironment favorable for tissue regeneration.

Hematological analysis showed pronounced reduction in inflammatory indicators, including white blood cell (WBC) and lymphocyte levels, in the D^ANet-DA group compared with the control group (Figure S30), further manifesting the alleviation of systemic inflammation. Because skin repair is closely associated with neovascularization within the wound bed [40, 41], the expression level of vascular endothelial growth factor (VEGF), a prototypical marker indicative of pro-angiogenic activity, was subsequently analyzed. Immunofluorescence staining revealed markedly enhanced angiogenesis in the D^ANet-DA group (Figure S31), suggesting its superior pro-regenerative efficacy in infected wound management. Moreover, all groups of mice displayed gradual increases in body weight throughout the treatment period (Figure S32), and no obvious inflammation or tissue damage was observed in major organs including heart, liver, spleen, lung, and kidney by histopathological observations (Figure S33). These results indicate that the therapeutic formulations cause no evident systemic toxicity (Figure S34). Overall, D^ANet-DA exhibits potent wound-healing therapeutic performance in the conventional *MRSA*-infected wound model, accompanied by enhanced antibacterial, anti-inflammatory, and angiogenic effects.

In addition to the conventional wound model, we further challenged D^ANet-DA in a more severe and clinically demanding scenario, namely, *MRSA*-infected burn wounds. Burn injuries cause approximately 180 000 deaths annually [42], and are typically associated with deep tissue damage, elevated oxidative stress, and increased susceptibility to multidrug-resistant infections and toxin-related complications [43, 44]. We therefore established a burn wound infection model and treated with D^ANet-DA (Figure 8A). First, the wound H₂O₂ level in the infected burn wounds was measured and found to be approximately 82 μ M (Table S3), exceeding the 50 μ M H₂O₂ concentration identified as optimal in vitro (Figure S5). Moreover, as mildly alkaline pH favors spontaneous DA-to-PDA polymerization [45, 46], the wound pH was also determined and found to be near-neutral to mildly acidic (6.5–7.0) (Table S3). This pH range suppresses spontaneous DA polymerization and nonspecific PDA formation while favoring G4/hemin-mediated DA oxidation in the presence of H₂O₂.

After D^ANet-DA treatment, wound healing monitoring demonstrated nearly complete closure on day 13, with a final healing rate of $99.0 \pm 0.5\%$, which was higher than that of the DNet-DA group ($86.6 \pm 1.4\%$) and vancomycin-treated group ($92.9 \pm 2.8\%$) (Figures 8B,C and S35A,B). The remaining treatment groups showed no apparent improvement in wound healing over the control group, among which the NIR-only group specifically confirmed that irradiation alone did not contribute to wound closure. Real-time infrared imaging was performed to monitor the in vivo photothermal response. Notable photothermal heating was observed only in the DNet-DA and D^ANet-DA groups under NIR illumination (Figure S36). Among all formulations, D^ANet-DA exhibited the strongest thermal response following 4 min of NIR exposure in vivo, with the macroscopic temperature at the wound site reaching 47.5°C, below the range generally leading

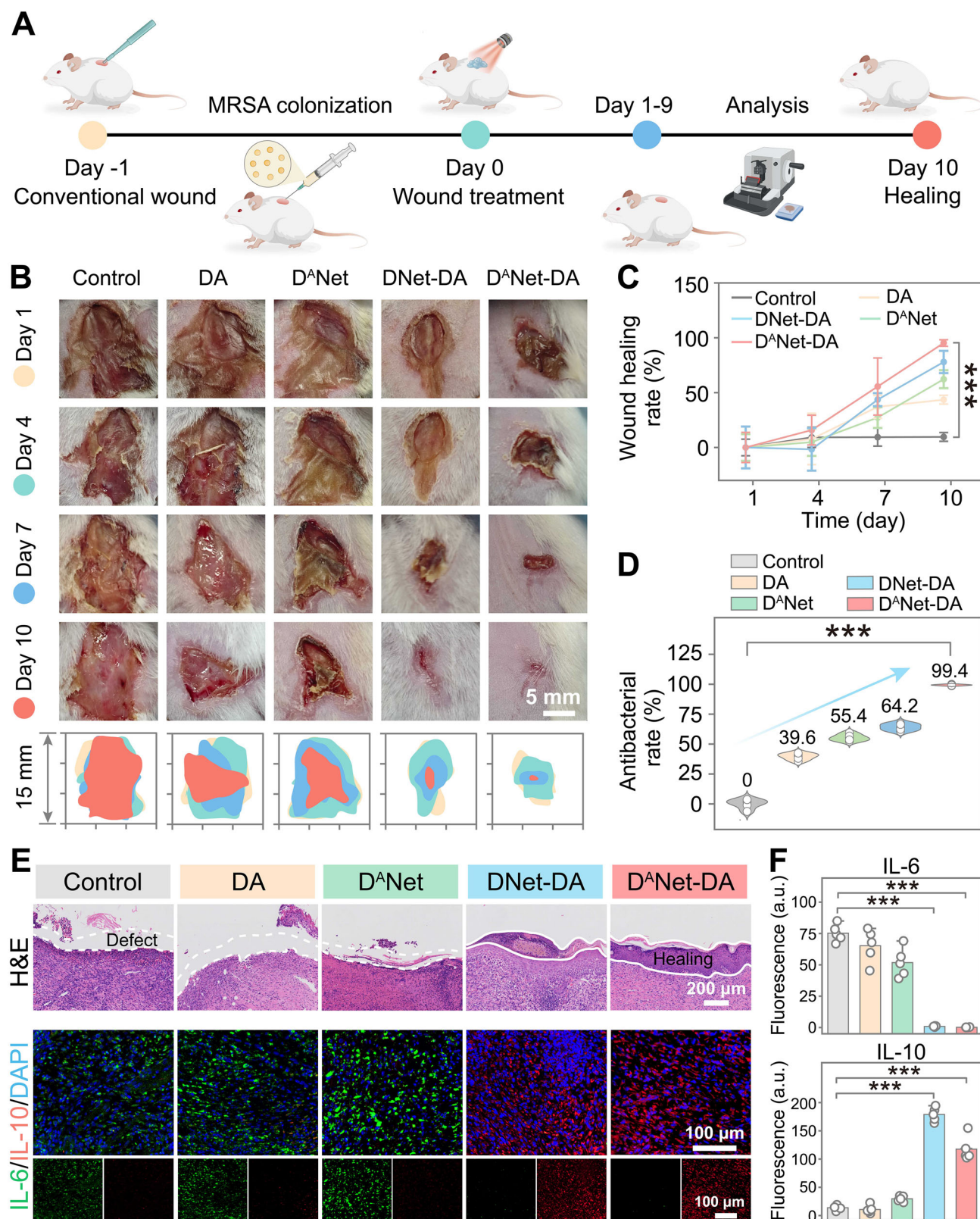


FIGURE 7 | In vivo treatment efficacy of D^ANet-DA in the MRSA-infected conventional wounds. (A) Schematic of MRSA-infected wound model and treatment regimen. (B) Representative images of infected wound sites in mice subjected to different treatments. (C) Analysis of the relative wound healing rate ($n = 5$, mean $\pm$ SD). (D) Antibacterial rates of different treatments in the infected wounds ($n = 5$, mean $\pm$ SD). (E) Representative H&E images showing tissue morphology and inflammation, and immunofluorescent images displaying IL-6 and IL-10 expression in cutaneous tissues after different treatments on day 10. (F) Quantitative analysis of IL-6 and IL-10 expression derived from immunofluorescent imaging ($n = 5$, mean $\pm$ SD). Statistical differences (p -values) are evaluated by one-way ANOVA with Tukey's multiple-comparisons test in C, D, and F. *** represents $p < 0.001$.

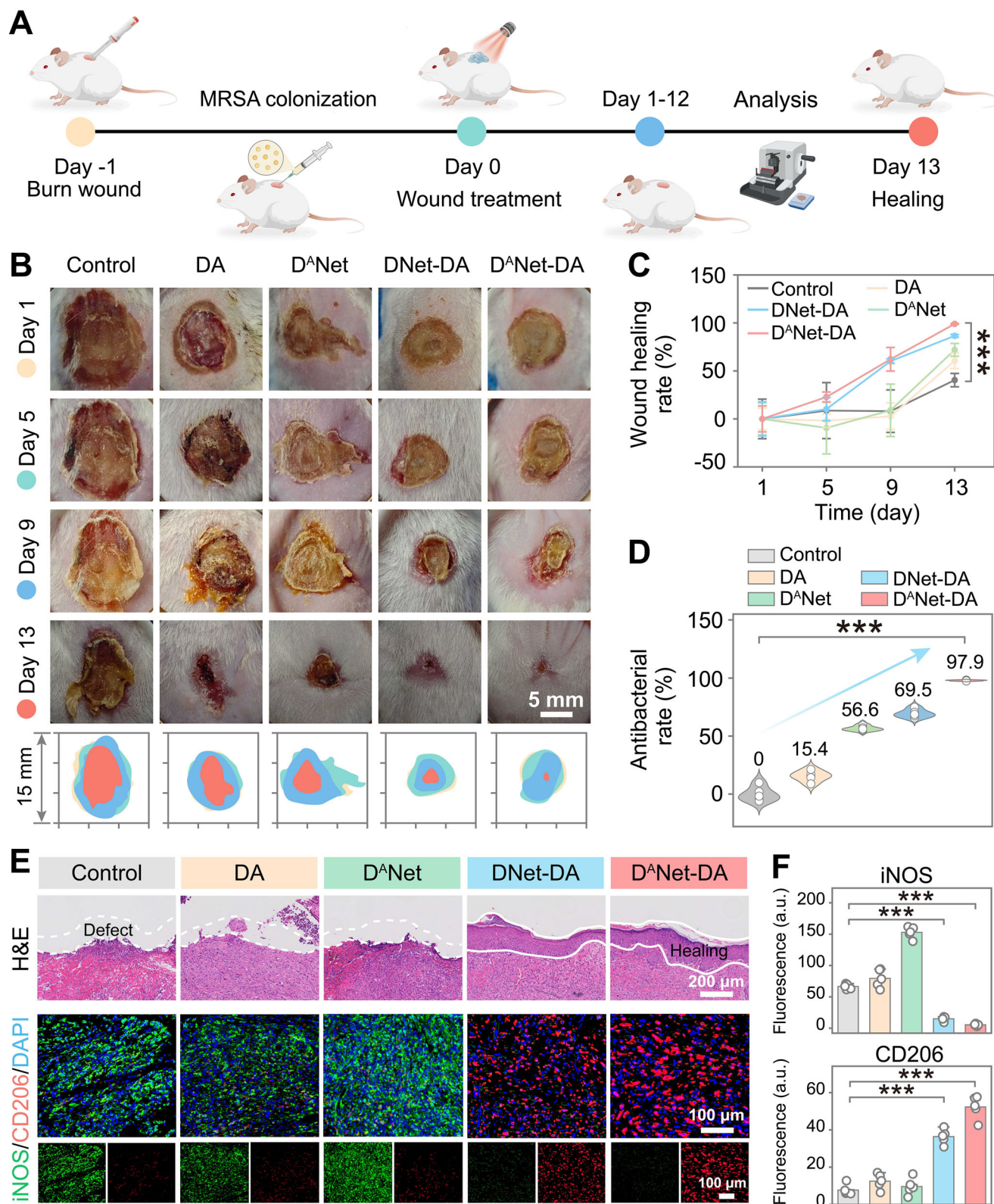


FIGURE 8 | In vivo treatment efficacy of D^ANet-DA in the MRSA-infected burn wounds. (A) Schematic illustration of MRSA-infected burn wound establishment and treatment regimen. (B) Representative images of infected burn wound sites in mice subjected to different treatments. (C) Analysis of the relative wound healing rate ($n = 5$, mean $\pm$ SD). (D) Antibacterial rates of different treatments in the infected burn wounds ($n = 5$, mean $\pm$ SD). (E) Representative H&E staining showing tissue morphology and inflammation, and immunofluorescent images displaying iNOS and CD206 expression in cutaneous tissues after different treatments on day 13. (F) Quantitative analysis of iNOS and CD206 expression derived from immunofluorescent imaging ($n = 5$, mean $\pm$ SD). Statistical differences (p -values) are evaluated by one-way ANOVA with Tukey's multiple-comparisons test in C, D, and F. *** represents $p < 0.001$.

to thermal tissue damage. Residual bacteria around the wound sites were further collected to evaluate the antibacterial efficacy (Figures 8D, S35C, and S37). Despite the relatively moderate macroscopic temperature, D^ANet-DA achieves efficient bacterial killing, with an antibacterial rate of $97.9 \pm 0.4\%$. This high antibacterial efficacy may arise from the close contact of the PDA nanoshell with bacterial surface, which enables localized heating sufficient for bacterial killing at the bacteria–PDA interface while maintaining a moderate temperature in the surrounding tissue. In comparison, the DA, D^ANet, and DNet-DA groups showed lower antibacterial rates of $15.4 \pm 4.6\%$, $56.6 \pm 2.1\%$, and $69.5 \pm 3.5\%$, respectively. Beyond antibacterial assessment, ELISA analysis further demonstrated that D^ANet-DA treatment substantially reduced the residual SED levels in infected burn wounds (Figure S38). In contrast, toxin levels remained significantly high after vancomycin administration despite its effective antibacterial activity. These results demonstrate that D^ANet-DA maintains potent antibacterial, toxin-removing, and wound-healing efficacy even in the more challenging burn wound infection model.

Further histological analysis on day 13 showed that D^ANet-DA treatment led to almost complete re-epithelialization and normalized granulation tissue formation in burn wounds (Figures 8E (top) and S39). Immunofluorescence staining revealed reduced expression of iNOS, a signature marker of M1 macrophages, together with an elevated expression of CD206, a signature marker of M2 macrophages, in the skin tissue following D^ANet-DA treatment, accompanied by accelerated wound healing (Figure 8E(bottom),F). Consistently, hematological profiling showed that D^ANet-DA treatment effectively restored physiological inflammatory balance (Figure S40), supporting its pronounced anti-inflammatory activity. The strongest VEGF signals were also observed in D^ANet-DA group (Figure S41), indicating significant pro-angiogenic effect during burn wound repair. Moreover, no signs of systemic toxicity occurred following D^ANet-DA administration, as supported by stable body weight and normal histological morphology of major organs (Figures S42 and S43). In particular, coagulation analysis revealed no appreciable changes in the measured coagulation parameters following D^ANet-DA treatment (Figure S44), suggesting that D^ANet-DA, unlike pathological NETs, exhibits a low procoagulant potential and, consequently, a limited propensity for thrombotic responses. Collectively, in vivo results from both conventional and burn wound infection models demonstrate that D^ANet-DA enables efficient bacterial eradication, inflammatory mitigation (Figures S35 and S45), thereby promoting neovascularization and ultimately facilitating wound tissue regeneration.

3 | Conclusion

In summary, we developed a NETs-mimetic dopamine-incorporated DNA net, termed D^ANet-DA, that couples targeted bacterial eradication with concurrent toxin neutralization for antibacterial therapy. Distinct from conventional bactericidal strategies that primarily focus on pathogen killing but often leave residual toxins unresolved, D^ANet-DA establishes an integrated trap-kill-neutralize therapeutic mode. Compared with previously reported NETs-inspired antibacterial and antitoxin strategies, D^ANet-DA advances three key features:

(i) specific bacterial recognition and trapping with minimal host–cell interactions; (ii) responsiveness to the wound microenvironment; and (iii) multifunctionality of a single PDA component for simultaneous bacterial killing and toxin clearance (Tables S5 and S6). Mechanistic studies demonstrate that this antibacterial–antitoxin strategy suppresses toxin-induced NF- κ B pathway activation, reduces oxidative stress and pro-inflammatory cytokine production, and promotes the formation of a pro-regenerative immune microenvironment. In vivo studies in both conventional and burn wound infection models further confirm that D^ANet-DA effectively eliminates MRSA, attenuates inflammation, enhances angiogenesis, and accelerates wound tissue regeneration. Overall, this work presents a programmable NETs-mimetic DNA biomaterial that transforms antibacterial therapy from pathogen eradication alone into coordinated pathogen clearance, toxin detoxification, and inflammation resolution, offering a promising design principle for treating wound infections and other bacterial infection-associated diseases.

Author Contributions

Jun Li: conceptualization, investigation, writing – original draft, methodology. **Hao Yang:** conceptualization, investigation, writing – original draft, writing – review and editing, methodology, funding acquisition, project administration, resources, supervision. **Shuangquan Lai:** data curation, formal analysis, methodology. **Ruijie Deng:** supervision, project administration, writing – review and editing, visualization. **Yi Deng:** conceptualization, funding acquisition, writing – review and editing, project administration, supervision, validation.

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Ethics Statement

All animal procedures were performed according to the ethical standards approved by the Animal Ethics Committee of Sichuan University (Approval No. WCHSIRB-AT-2025-578).

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Research data are not shared.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.

Supporting File: anie75263-sup-0001-SuppMat.docx.