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REVIEW

New Strategies for the Treatment of Diabetic Foot Ulcers Using Nanoenzymes: Frontline Advances in Anti-Infection, Immune Regulation, and Microenvironment Improvement

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Abstract: Diabetic foot ulcers are one of the most serious consequences of diabetes, arising from vascular impairment of the skin and disturbances in the microenvironment. This condition involves pathological changes such as wound infection, hyperglycemia, hypoxia, oxidative stress, and cellular dysfunction, necessitating multifaceted interventions. Traditional treatments often target only the wound itself, resulting in limited effectiveness. In contrast, nanoenzymes offer a promising therapeutic option due to their excellent biocompatibility and tissue permeability. They exhibit higher catalytic efficiency, optimal size and structure, and improved stability compared to natural enzymes. Encapsulating various nanoenzymes within novel biomaterials can enhance therapeutic outcomes through antibacterial action, glycemic control, oxygen delivery, antioxidative effects, anti-inflammatory properties, and angiogenesis promotion. This approach represents a key direction for future diabetic wound treatment. This article summarizes the role of nanoenzymes in diabetic wound management and discusses the potential mechanisms of their action. We also provide an outlook on their application prospects, aiming to advance their clinical utilization.

Keywords: chronic wound, hyperglycemia, oxidative stress, antibacterial action, angiogenesis

Introduction

Diabetes is a serious long-term disease, with 425 million people currently diagnosed. By 2045, the prevalence is expected to rise to 700 million.[1,2] Up to 25% of patients with diabetes develop diabetic foot ulcers (DFUs), which are among the most common complications of the condition.[3] DFUs generally manifest as difficult-to-heal lesions on the feet and legs, marked by an exceedingly protracted or stagnant wound healing process (hemorrhage, irritation, growth, and remodeling).[4] Furthermore, DFUs are often accompanied by severe infections, leading to prolonged non-healing of wounds. Approximately half of DFU patients experience lower limb amputations, which is 15 times more than non-diabetic patients.[5] Individuals with concurrent DFUs have a higher mortality risk compared to those who do not have these ulcers.[6] The spatiotemporal coupling of pathological wound microenvironments characterized by hyperglycemia, hypoxia, infection, and excessive oxidative stress is a fundamental reason for the challenges in treating DFUs.[7] Patients with DFUs suffer from physical, psychological, and economic trauma, imposing an enormous strain on public health and healthcare systems.

Based on the characteristics of DFUs, standard clinical treatments include surgical debridement, offloading, antibiotic therapy, and wound dressings.[8] Unfortunately, prolonged and repeated debridement can cause significant pain and financial burden for patients. Additionally, the emergence of drug-resistant microorganisms may render antibiotics

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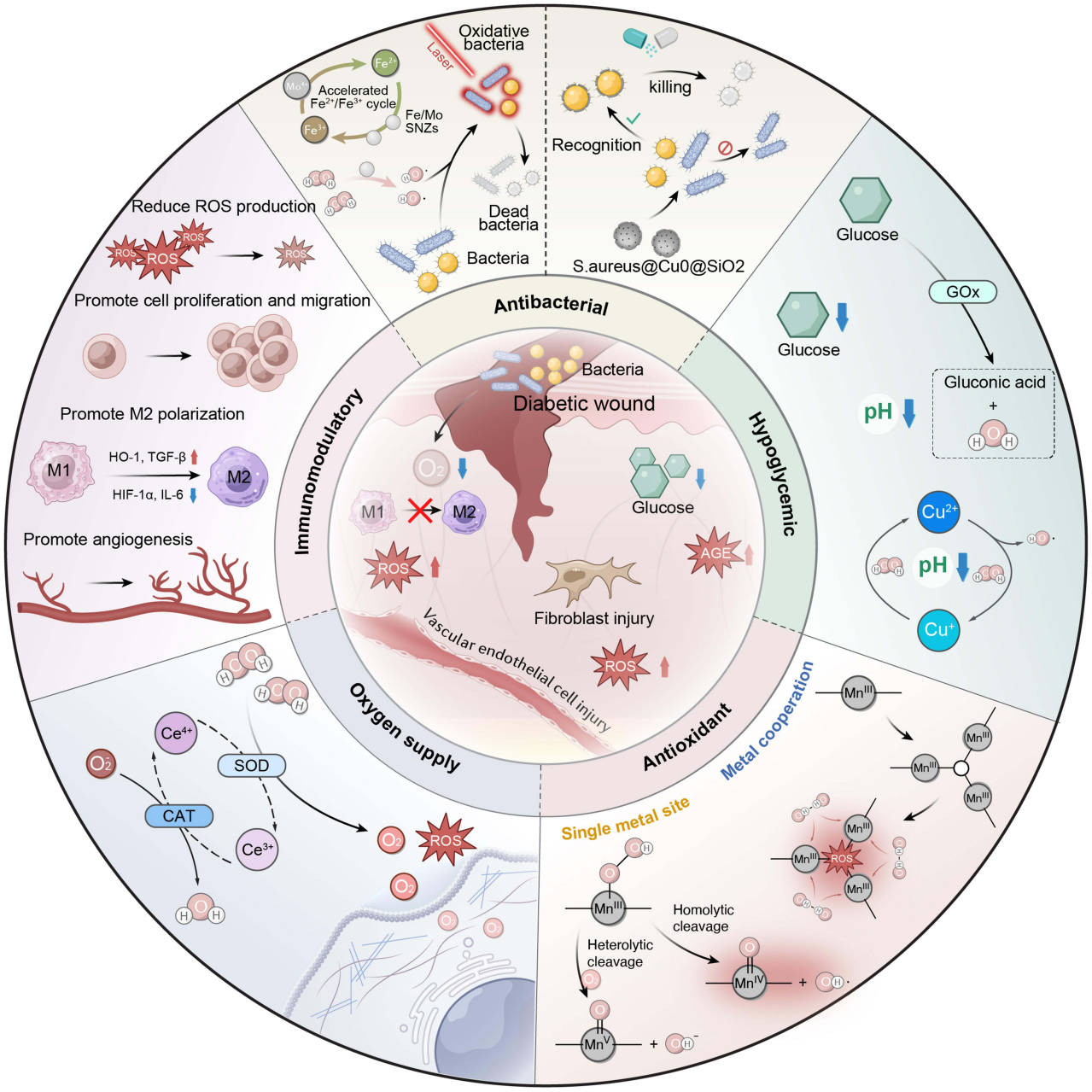
Graphical Abstract



ineffective. Traditional dressings tend to be functionally limited, requiring frequent changes and failing to adequately address issues such as hyperglycemia, hypoxia, and excessive oxidative stress in the wound microenvironment.[9] Consequently, numerous studies are focused on efficiently eliminating various antibiotic-resistant microorganisms through multiple approaches,[10,11] proposing a range of complex strategies to remodel the pathological wound microenvironment, including glucose regulation,[12] localized oxygen delivery,[13,14] photothermal and photodynamic antimicrobial therapies,[15] and reactive oxygen species (ROS) clearance.[16,17] Numerous multifunctional biomaterials, including electrospun nanofibers and hydrogels, have been developed to improve the pathological microenvironment and facilitate the restoration of the healing cascade in chronic wounds.[18–20] These topical formulations minimize the toxic effects

associated with renal or oral administration, thereby enhancing patient comfort and therapeutic efficacy.[21] Although these approaches partially address the shortcomings of traditional dressings, their efficacy in microenvironment remodeling is constrained by factors including low tissue permeability, inadequate biocompatibility, and delivery challenges.

Recent studies indicate that enzymes and their analogs significantly enhance the process of wound healing.[20,22] The human body comprises multiple natural enzymes that collaboratively sustain the stability of the wound microenvironment. When the environment is disrupted, these natural enzymes participate in tissue repair through multiple cascading reactions. For example, glucose oxidase can lower local blood sugar levels,[23,24] while endogenous antioxidant enzymes, such as catalase and superoxide dismutase, can eliminate ROS and generate oxygen,[25,26] thereby promoting the polarization of macrophages toward an antioxidant phenotype.[27] However, natural enzymes are highly sensitive to reaction conditions and environmental factors. Their limitations in terms of direct human application and high costs hinder their development and widespread use.

Nanoenzymes, as a class of enzyme mimetics, exhibit unique properties that combine those of nanomaterials and catalysts.[28] They are specialized nanomaterials designed to simulate enzymatic processes, capable of accelerating the conversion of substrates into products under physiological conditions.[29] Advancements in nanotechnology have led to the identification of over 50 distinct nanomaterials exhibiting enzyme-like catalytic activity,[30] including metal oxides,[31] noble metal nanocrystals, selenides,[32] phosphides,[33] nitrides, polymer-metal complexes,[34] and metal-organic frameworks (MOFs).[35] Compared to natural enzymes, nanoenzymes offer higher catalytic efficiency, more favorable size and structure, and greater stability, making them widely applicable in fields such as catalysis, environmental science, and biomaterials.[22] Simultaneously, nanoenzymes can be delivered using biodegradable, safe, and highly stable carriers, leveraging the advantages of nanotechnology for controlled release, effectively addressing the spatiotemporal limitations of natural enzymes.[36,37]

However, the large-scale industrialization of nanoenzymes remains challenging, primarily due to the inability of their types and structures to achieve precise matching with diverse therapeutic needs.[38] Therefore, it is essential to possess a thorough understanding of the physiological mechanisms of diseases and the practical clinical requirements from the outset of nanoenzyme design. This knowledge will enable the development of categorized biological materials tailored to the physicochemical properties of different nanoenzymes, thereby addressing various wound-related issues more effectively.

In this article, we summarize the diverse pathogenic pathways implicated in the recovery process of DFUs and their contributions to wound healing. We innovatively present a new perspective on the functions of nanoenzymes, integrating the challenges faced in clinical practice and outlining the diverse biological functions of nanoenzymes in response to different pathophysiological changes. Furthermore, we provide an overview of the current infection control strategies utilizing nanoenzymes in wound dressings and their potential applications in wound healing, introducing a novel classification based on whether the bactericidal action of nanoenzymes is dependent on reactive oxygen species. We discuss the potential mechanisms through which different types of nanoenzymes affect the wound microenvironment and cellular physiological functions. Ultimately, we highlight the obstacles and prospective pathways for the development and application of nanoenzyme dressings for clinical use.

Wound Characteristics of Diabetes

Compared to other types of chronic wounds, DFUs have a complex microenvironment and more intricate pathogenic mechanisms. Factors such as recurrent bacterial infections, hyperglycemia, accumulation of ROS, hypoxia, dysregulation of cytokine and growth factor expression, impaired angiogenesis and persistent inflammation all hinder the healing process. These factors can prolong one or more stages of wound healing (toxic hydroxyl radicals, irritation, growth, and remodeling), thereby increasing the difficulty of clinical treatment for diabetic wounds.[36,39]

Wound Infection

Infection is one of the critical risk factors for poor wound healing in diabetic patients. Diabetic foot infections can be caused by single bacteria, such as Staphylococcus aureus, or by mixed infections involving multiple microorganisms, including Staphylococcus, Streptococcus, Enterococcus, Escherichia coli, Candida albicans, and others. The pathogenic

bacteria vary widely in type and severity.[40] The prevalence of antibiotic-resistant strains, specifically methicillin-resistant Staphylococcus aureus (MRSA), is steadily increasing, now accounting for 30% to 40% of all patients with diabetic infections.[41] AMR, various microbial populations from the external environment, primarily bacteria, can colonize wounds and further promote the formation of biofilms.[42] These biofilms serve as a protective barrier for the microorganisms, hindering immune cells from eliminating them and enabling evasion of host defenses. Biofilms formed by the adhesion and accumulation of multiple microorganisms are inherently more challenging to treat than those produced by a single species. Notably, Streptococcus pyogenes invades exposed wound surfaces by harboring genes that encode a range of virulence factors, including toxins, enzymes, and adhesins.[43] Concurrently, Staphylococcus aureus synthesizes numerous surface proteins that facilitate recognition and adhesion to host tissue during the early stages of infection, thereby significantly complicating the treatment of wound infections.[44] Without timely intervention, pathogenic bacteria can penetrate deep into the fascia, leading to life-threatening sepsis, which places diabetic ulcer patients at a high risk of amputation.

Furthermore, post-amputation trauma intensifies, and the patient's immune response diminishes, hence heightening the chance of post-surgical infections and establishing a detrimental cycle of "infection-amputation-infection." Consequently, it is imperative to manage infections promptly and preserve the damaged limb to enhance outcomes.[45]

Hyperglycemia

Hyperglycemia is a characteristic feature of the microenvironment in DFUs and is linked to insulin insufficiency or resistance. Under typical circumstances, the body regulates blood glucose levels via hormonal and neurological mechanisms.[46] However, in pathological processes, blood glucose levels can rise and accumulate, leading to the induction of various pathological conditions.

In diabetic individuals, heightened blood glucose levels can readily lead to an accumulation of advanced glycation end products (AGEs), which subsequently exacerbate cellular or tissue damage. AGEs attach to the receptor for advanced glycation end products (RAGE) on cell membranes, triggering downstream signaling cascades that elevate oxidative stress and provoke chronic inflammation, so impeding the wound healing process.[47]

Localized hyperglycemia concurrently restricts the proliferation and migration of epithelial cells and fibroblasts, thereby restricting cell proliferation and remodeling processes.[48] Elevated blood glucose levels supply ample nutrients for bacteria, significantly enhancing the likelihood of infection.[49,50]

Excessive Oxidative Stress

ROS primarily include hydroxyl radical (·OH), hydrogen peroxide (H_2O_2) and superoxide anion (O_2·–), which can be continuously produced during the normal metabolic processes of organisms.[51] The unregulated buildup of ROS is a characteristic feature of the pathological milieu in DFUs, resulting in considerable inhibition of endogenous stem cell viability, extracellular matrix (ECM) production, and growth factor activity.[52]

Moreover, continuous exposure of the wound to high levels of ROS induces pro-inflammatory factors, exacerbating wound inflammation and causing failure in the phenotypic transition of macrophages from M1 to M2 states, thereby delaying the regenerative process.[53] Early infection-induced inflammation can even trigger a localized inflammatory storm, resulting in excessive endogenous ROS production and further disrupting the balance of the wound microenvironment.[54] The atypical generation of ROS has been recognized as a crucial mediator in the pathophysiology of inflammation.

Localized Tissue Hypoxia

Oxygen plays a crucial role in almost every phase of reactive damage and the wound healing cascade, rendering sufficient oxygen supply essential for the healing process. In diabetic wounds, increased oxygen consumption by local metabolic oxygen depletion, inflammatory cells, and bacterial overload can lead to chronic hypoxia.[55]

Growing data indicates that hypoxia worsens the already impaired diabetic microenvironment. Prolonged hypoxia in chronic wounds adversely affects the production of vascular endothelial growth factor (VEGF), hence hindering angiogenesis and wound healing. The nutrients and oxygen essential for healing in newly formed wounds rely on the

supply from newly established and regular blood vessels. A reduction in the number of endothelial cells in diabetic wounds decreases the quantity of neovascularization and alters the function of normal vessels, further exacerbating localized tissue hypoxia. This vicious cycle significantly delays the healing of the wound.[56]

Consequently, enhancing the dysregulated physiological state in diabetic wounds and augmenting oxygen supply are efficacious techniques for addressing significant tissue damage induced by diabetes.

Changes in Cellular Biological Functions

Diabetic wounds are characterized by alterations in various cellular biological functions, leading to persistent chronic inflammation and delays in the proliferation and remodeling stages. Macrophages, vascular endothelial cells and fibroblasts significant roles in wound healing.

Dysregulation of macrophage phenotypes is a major reason for the prolonged inflammation seen in diabetic wounds. Macrophages are categorized into two primary types: the standard M1 lineage, characterized by pro-inflammatory actions, and the alternative M2 lineage, which demonstrates an anti-inflammatory phenotype.[57] Subsequent to homeostasis, M1 macrophages swiftly migrate to the injury site and engage in pathogen phagocytosis by eliminating or clearing injured cells during the inflammatory phase. Subsequently, the macrophage population transitions from M1 to M2, with M2 macrophages being essential for subsequent vascular regression and remodeling.[58]

However, in the microenvironment of diabetic wounds, factors such as hyperglycemia and infection disrupt cellular homeostasis, leading to immune dysregulation. This results in an excess of immune cells and pro-inflammatory cytokines, accompanied by defects in the M1 to M2 transition.[59] M1 macrophages continue to release pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), monocyte chemotactic protein-1 (MCP-1), and interferon-gamma (IFN-γ), which prolong the inflammatory phase and delay wound healing.[60,61]

The diminished quantity of M2 macrophages and the increased M1/M2 ratio result in a deficit of essential growth factors, including VEGF, platelet-derived growth factor(MD), and so on, alongside anti-inflammatory cytokines such as transforming growth factor-β (TGF-β) and interleukin-10 (IL-10), which are vital for the proliferation and remodeling phases.[62] Among these, TGF-β is a peptide member of the transforming growth factor-beta (TGF-β) superfamily of cytokines. TGF-β reverses and inhibits stimulation of macrophages by blocking signal transduction through receptor pathways.[63] Interleukins, produced by blood monocytes and tissue macrophages, are important inflammatory molecules; specifically, IL-10 has been shown to significantly accelerate the healing process by promoting re-epithelialization and angiogenesis.[64]

Fibroblasts primarily promote wound healing by enhancing granulation tissue formation, remodeling the ECM, and facilitating angiogenesis.[65,66] However, in the diabetic wound microenvironment, fibroblasts undergo phenotypic changes and functional dysregulation. Research indicates that factors such as hyperglycemia, hypoxia, and chronic inflammation can cause fibroblasts to exhibit abnormal functional behaviors and phenotypic transformations during wound healing, thereby impeding the healing process.[48]

Vascular endothelial cells are critical for the formation of blood vessels in wounds, and their functions are regulated by various cytokines, including PDGF, epidermal growth factor (EGF), TNF-α, VEGF, and angiopoietins, as well as anti-angiogenic factors like platelet factor 4(PF-4), thrombospondin 1(TSP-1), tissue inhibitor of metalloproteinases 2(TIMP-2) and endostatin.[67,68] Among these, PF4, also known as chemokine ligand 4, possesses angiogenesis-inhibiting properties.[69] TSP1 is a member of the classical platelet reaction protein subfamily and is the first identified endogenous angiogenesis inhibitor.[70] TIMP-2 is a key regulatory protein composed of 194 amino acids, with a molecular weight of approximately 21 kDa, primarily responsible for reducing the activity of matrix metalloproteinases.[71] In the wound microenvironment of healthy individuals, fibroblasts can release VEGF to activate endothelial cells (ECs), leading to enhanced secretion of proteolytic proteins. Subsequently, elevated levels of matrix metalloproteinases (MMPs) from macrophages and proteolytic enzymes facilitate the degradation of basement membranes, the migration of endothelial cells, and the angiogenic sprouting of new blood vessels into the wound. The recruitment of vascular smooth muscle cells (VSMCs) and pericytes further supports angiogenesis.[72] However, in chronic non-healing wounds, the balance of cytokines is disrupted under the stimulus of chronic inflammation, resulting in insufficient VEGF secretion and hindered

cell migration, which further obstructs the formation of new blood vessels.Consequently, reinstating the normal physiological functioning of cells is especially vital during the initial phases of wound healing.

However, upon reviewing the current landscape of traditional treatments, no single approach effectively addresses the issues of slow, difficult, and poor healing of diabetic wounds. From the perspective of treating chronic wound infections, current strategies primarily centered on antibiotic use do not adequately resolve issues related to microbial resistance and biofilm formation.[73] When considering the improvement of the microenvironment in diabetic wounds, treatments such as hyperbaric oxygen therapy for hypoxia,[74] the use of VEGF, EGF,[75] stem cell therapies,[76] or local blood glucose control[77]—though clinically relevant—often function in isolation and can be costly with limited effectiveness in many cases.

In contrast, nanoenzymes can effectively tackle microbial resistance and exert multiple biological functions through multi-target action. Therefore, research and synthesis of the physicochemical properties, biological functions, and mechanisms of action of nanoenzymes hold significant practical importance.

The Role of Nanoenzymes in Diabetic Wound Healing

Nanoenzymes are nanomaterials with excellent enzyme-like activity, characterized by adjustable catalytic activity, multi-functionality, and high stability. Traditional preparation methods for nanoenzymes primarily involve physical binding and chemical synthesis. Physical methods can be further divided into physical mixing and physical vapor deposition (PVD). The former is straightforward but may result in weaker interactions between the nanomaterials and auxiliary materials, potentially affecting the stability and catalytic efficiency of the nanoenzymes. In contrast, PVD involves evaporating metals or metal compounds and depositing them onto a substrate, allowing for precise control over the composition and thickness of the nanomaterials, although it requires sophisticated equipment.[78] Chemical methods mainly include sol-gel processes and chemical precipitation, both of which are significantly influenced by reaction conditions (such as temperature, reactant concentration, and stirring speed), necessitating strict control over these parameters.[79]

In recent years, with advancements in technology, composite assembly methods have gained attention for producing more powerful and versatile nanoenzymes. Liu and his team employed genetic engineering strategies to integrate ionizable repeating histidine-glutamic acid sequences onto the outer surface of human ferritin nanocages. Utilizing the tetravalent structure, they ingeniously designed tetravalent cascade nanoenzymes with multiple enzyme-like activities, significantly enhancing the reaction rates of the nanoenzymes.[80] Additionally, to address the challenge of nanoenzyme reusability and further improve safety, Simms and his team reported a novel method for synthesizing nanoenzymes under mild, safe, and environmentally friendly aqueous conditions, reliably yielding water-stable and highly efficient nanoenzymes.[81]

These various preparation methods for nanoenzymes lay a solid foundation for their safer and more efficient performance in various biological functions. The successfully synthesized nanoenzymes primarily promote the healing of chronic wounds associated with diabetic foot ulcers through five key mechanisms.

Antibacterial Effects

The widespread use of antibiotics has resulted in a significant threat to human health due to antimicrobial resistance (AMR). There is an urgent need to explore effective strategies to mitigate the spread of AMR. Concurrently, traditional antibacterial methods demonstrate limited efficacy in treating chronic wounds, often struggling to penetrate bacterial biofilms and thereby failing to effectively eliminate the bacteria.[82] Antimicrobial nanoenzymes, owing to their extensive antibacterial efficacy and enzyme-like catalytic function, have emerged as formidable instruments in combating anti-microbial resistance (AMR). The swift advancement of nanotechnology has introduced novel alternatives for addressing bacterial diseases.

Five categories of antimicrobial nanomaterials have been extensively reported, including metal nanoparticles (NPs) such as Ag, Cu, Au, ZnO, La_2O_3, CeO_2, and V_2O_2; carbon-based nanomaterials like carbon nanotubes (CNT), graphene, and graphene oxide (GO); borides such as BN; nanopolymers like polycarbonate; and nanocomposites such as La_2O_3/Ag-GO. These materials have been widely studied for their antibacterial properties.[83,84]

Transition metal-based nanoenzymes, such as those containing Cu, Mn, and Zn, can induce irreparable oxidative damage to bacterial proteins, DNA, and RNA, leading to lipid membrane damage at sites of bacterial infection.[3] Based

on their mechanisms of action, nanoenzymes can be classified into two main categories: those that rely on ROS for bactericidal activity and those that do not.

ROS-Dependent Mechanisms

In recent years, the use of nanoenzymes to mimic peroxidase (POD) activity by converting hydrogen peroxide (H_2O_2) into more inevitably inflicts harm (·OH) for bacterial killing has garnered significant attention.[85] This strategy allows for a substantial reduction in the concentration of applied H_2O_2, thereby minimizing potential side effects, and has become a widely accepted approach for treating bacterial infections.

The intrinsic non-selectivity of ROS in differentiating normal microbiota from pathogenic bacteria diminishes the requisite selectivity for nanoenzymes to be deemed excellent antibacterial agents. Current research is focused on implementing various responsive mechanisms to control the timing, quantity, and localization of ROS production, enhancing the precision of antibacterial action while mitigating undesired effects on the normal microbial population.

Regulation of Nanoenzyme Reaction Timing

To mitigate collateral damage, the targeting of nanoenzymes can be adjusted. Some nanoenzymes achieve precise localization through responses to external stimuli such as light and acidic microenvironments. Under light stimulation, nanoenzymes can enhance their catalytic activity, exhibiting a broad antibacterial spectrum and high spatiotemporal controllability.

Some strategies involve enhancing the photothermal performance of nanoenzymes by utilizing co-catalytic reactions among various elements. Song and his team successfully synthesized a multifunctional nanoenzyme composed of molybdenum sulfide (MoS2) and iron sulfide (FeS2) by hydrothermal method. A series of experiments showed that this nanozyme with iron and molybdenum as the main functional components could successfully trigger the Fenton reaction to achieve the ideal peroxidase (POD) mimetic activity. The synergistic effect of the two is reflected in that the CO catalytic reaction of mo4+/mo6+ redox pair significantly accelerates the conversion of fe2+/fe3+ and thus improves the efficiency of chemodynamic therapy (HMMo-Sazyme). In addition, this nanozyme can induce local temperature rise by introducing near-infrared (NIR) laser for photothermal therapy (PTT). At the same time, under the stimulation of high temperature, the oxidative activity is further enhanced, showing excellent antibacterial activity[86] He and his team functionalized Pt nanoparticles (Pt-NP) on V2C MXene-based nanomaterials and discovered that this combination exhibits a plasmon resonance effect. Subsequent experiments demonstrated an enhanced photothermal conversion efficiency of 59.6% and prolonged laser irradiation in the NIR-II region, providing a viable approach to improve the photothermal performance of nanoenzymes.[87] Du and his team synthesized a defect-rich hybrid nanoenzyme, MoWS2, using a hydrothermal method and further enhanced its activity through overheating. In vitro antibacterial assays demonstrated that MoWS2 effectively achieves bactericidal activity and biofilm removal through the generation of high temperatures and ROS.[88]

Another strategy involves improving molecular structures to enhance photothermal efficiency. Gao and his team developed Cu_2O-SnO_2 doped polydopamine (CSPDA) triphase yolk-like antimicrobial nanoenzymes, which exhibit high photothermal conversion efficiency and Fenton-like peroxidase effects for photothermal and chemokinetic antibacterial therapy[89] (Figure 1). Lou and his team innovatively utilized triazine-based TP-TA COF to mimic amino acid residues, designing hydrophobic voids around the active site. This approach significantly increased the intermolecular contact area, thereby endowing the composite material with exceptional photothermal properties.[90] Zhou and his team prepared an ultrathin PdMo bimetallic nanosheet enzyme, whose atomically thin structure endows it with a high specific surface area, abundant active sites, excellent conductivity, and maximized atomic efficiency. Under laser irradiation, it exhibits remarkable photothermal and peroxidase-like activities, demonstrating significant bactericidal effects and biofilm degradation efficiency.[91]

Cao and his group used photoreduction and solvothermal processes to create a unique Ag/Bi_2MoO_6 (Ag/BMO) nanoenzyme. This enzyme, which was enhanced by charge separation engineering, has NIR-II photodynamic characteristics and light-activated sustainable peroxidase mimetic activity. With a kill rate of almost 99.9%, the Ag/BMO nanoenzyme has remarkable bactericidal activity against methicillin-resistant MRSA. The remarkable antibacterial

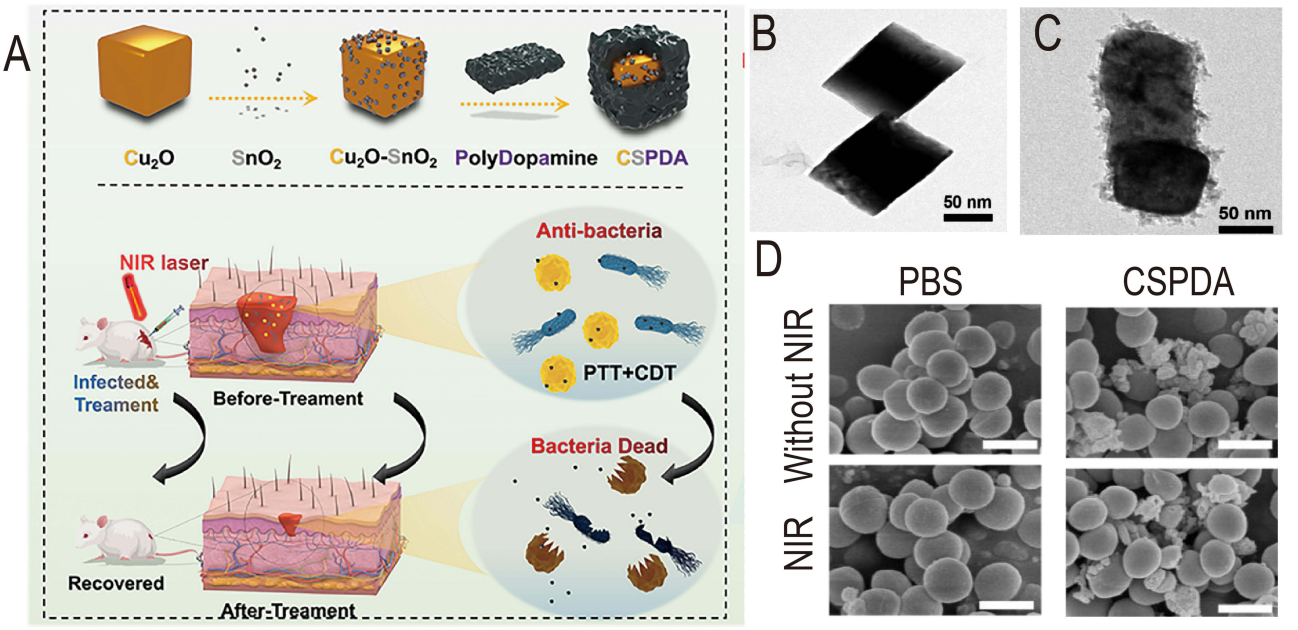


Figure 1 (**A**) A schematic diagram of the synthesis, mechanism, and functional overview of CSPDA in synergistic antibacterial therapy combining PTT and CDT. (**B** and **C**) TEM images of Cu2O-SnO2,CSPDA. (**D**) SEM imaging of Staphylococcus aureus after different treatments.(NIR: 1.4 W ·cm−2 ·s-1, CSPDA: 50 μg·mL−1, Scale bars: 2μm). Reprinted from *Acta Biomater.* Volume 173, Gao J, Yan Y, Gao S, et al. Heterogeneous Cu(2)O-SnO(2) doped polydopamine fenton-like nanoenzymes for synergetic photothermal-chemodynamic antibacterial application. 420–431, Copyright 2024, with permission from Elsevier.[89]

capabilities of Ag/BMO NPs result from the synergy of peroxidase-like activity, NIR-II photodynamic behavior, and acid-facilitated Ag release. Theoretical studies suggest that the incorporation of Ag into BMO promotes the segregation of light-induced electron-hole pairs, thereby producing ROS and augmenting peroxidase-like enzymatic activity and NIR-II photodynamic efficacy according to the Russell mechanism.[92]

In addition to relying on external light for localization, nanoenzymes can respond to the acidic microenvironment of diabetic wounds by exhibiting catalase-like activity at specific sites, generating substantial amounts of ROS to effectively eliminate bacteria. Iron phosphate ($FePO_4$) nanoenzymes exhibit POD activity when subjected to acidic conditions and elevated H_2O_2 concentrations. In addition to relying on external light for localization, nanoenzymes can leverage the localized acidic environment of diabetic wounds as an anchor to express catalase-like activity at specific sites, generating substantial amounts of ROS to effectively eradicate bacteria. Jiang and his team immobilized CeO_2 and ZnO_2 onto scallop shell-derived FePOs nanoenzyme materials, creating a multifunctional cascade nanoparticle system through the synergistic interaction of these three components.The iron phosphate (FePOs) nanoenzyme can express peroxidase (POD) activity under the dual stimulation of an acidic environment and high concentrations of H_2O_2, facilitating the targeted release of the composite nanoenzyme. Concurrently, the H_2O_2 concentration can promote the self-activation reaction of ZnO_2, further enhancing the release of ROS from FePOs, leading to amplified oxidative stress, cellular membrane damage, and DNA disruption. CeO_2 can mitigate excess ROS by transitioning from the Ce4+ to the Ce3+ oxidation state, thereby enhancing its capacity to combat chronic inflammation and oxidative stress, which promotes the regeneration of surrounding infected tissues. This approach enhances ROS levels at the infection site while simultaneously eliminating excess ROS, thereby maximizing the eradication of bacterial biofilms and safeguarding normal tissues from oxidative damage. The research data from the team indicates that this nanoenzyme material only releases sufficient reactive oxygen species at a pH of 6.5. Under other acidic pH conditions, the activity of this nanoenzyme is significantly reduced. Therefore, the nanoenzymes exhibit strong stability and are less likely to be accidentally released in acidic environments outside the target area of diabetic wounds, thereby ensuring therapeutic efficacy and demonstrating fewer side effects.[93]

Li and his team engineered and synthesized an acid-responsive, hydrogen peroxide (H_2O_2)-self-sufficient Fenton catalyst comprising Cu-Fe ELC peroxides (CFE). Under acidic conditions at the infection locus, these nanoparticles decompose, liberating free copper ions, iron ions, ELC, and H_2O_2, thereby instigating a synergistic Fenton reaction and

copper adsorption. The liberated Cu and Fe ions work in concert to enhance the Fenton reaction via a Cu-Fe conversion cycle (Cu to Cu^{2+} and Fe^{3+} to Fe^{2+}), augmenting the concentration of bioactive •OH at the infection site. Importantly, ELC markedly extends the toxicity of Cu^{2+} by facilitating the transport of excess Cu^{2+} into bacteria, thereby inducing copper poisoning.[94] Zhang and his team synthesized a hollow mesoporous molybdenum single-atom nanoenzyme (HMMo-SAzyme) via a regulated chemical etching technique and pyrolysis approach. This nanoenzyme is encapsulated in a hyaluronic acid layer. Upon entering the wound, the abundant hyaluronidases present in the infected microenvironment degrade the outer hyaluronic acid, thereby exposing HMMo-Sazyme to the acidic environment. This acidic condition significantly enhances the catalytic activity of HMMo-Sazyme, facilitating the further conversion of H_2O_2 into •OH to eliminate bacteria.[95]

However, it is undeniable that the targeting specificity of these methods remains insufficient. How can drug design be optimized to enhance the targeting capability of nanoenzymes? What strategies can be employed to increase the pH sensitivity of nanoenzymes? Is it feasible to utilize antibody-mediated targeting to facilitate the synthesis of nanoenzymes? These questions require further investigation.

Regulation of Nanoenzyme Reaction Timing

In addition to the aforementioned strategies, some nanoenzymes can achieve more sensitive reactivity and precise localization by leveraging the responsiveness of platelets to wounds. Platelets, as a principal category of circulating blood cells, demonstrate multifunctionality in various microenvironments, including wound healing, inflammation, hemostasis, angiogenesis and in their specific binding to biological threats, such as bacteria, due to the diverse receptors present on their surfaces. These attributes render platelet membranes suitable vehicles for encapsulating nanomaterials and pharmaceuticals, presenting extensive potential applications in the management of inflammation and bacterial infections. Shi and his team developed a bio-organic nanoenzyme by encapsulating a FeZn-based bimetallic metal-organic framework (MOF) (MIL-88B-Fe/Zn) within a platelet membrane (PM@MIL-88B-Fe/Zn). Utilizing the propensity of platelets to aggregate at wound sites, this approach facilitates the targeted delivery of the nanoenzyme. Additionally, the presence of Zn modulates the electronic structure of Fe, further enhancing the catalytic kinetics of Fe's peroxidase-like activity, which generates potent ROS to effectively kill bacteria. This technique effectively resolves the issues of inadequate biodegradability, restricted targeting capability, and low reactivity of nano-catalysts in therapeutic applications within the wound microenvironment.[96]

Moreover, it is noteworthy that nanoenzymes can achieve targeted localization through the recognition of specific biomolecular expressions.For example, nanoenzymes can utilize the differential expression of alkaline phosphatase (ALP) in pathogenic Escherichia coli and non-pathogenic Staphylococcus aureus to achieve precise and on-demand bacterial killing. Zhuang and his team created an innovative CuO nanoenzyme system that utilizes the physiological circumstances of bacteria, characterized by elevated ALP expression, to activate an ALP-triggered ROS prodrug system. In this system, sodium 2-phosphate-L-ascorbate (AAP) catalyzes the production of ascorbic acid (AA) in pathogenic bacteria. The CuO NPs, which possess intrinsic ascorbic acid oxidase and peroxidase-like activities, convert AA into ROS, thereby enabling targeted elimination of bacteria.[97]

Glutathione (GSH), a powerful antioxidant, is essential in facilitating oxidative defense mechanisms against bacterial infections. Consequently, locally overexpressed GSH functions as an appropriate biomarker for identification. Thus, certain nanoenzymes can detect and eradicate GSH in the wound microenvironment, instigating a ROS surge that markedly improves antibacterial effectiveness. Liu and his team successfully synthesized a nanoenzyme-based copper-intercalated α-MoO_3 nanobelt. The MoO_3-x/Cu nanobelt, containing 2.11% copper, demonstrates increased POD catalytic activity and GSH depletion, efficiently depleting GSH in bacteria and markedly enhancing bactericidal effectiveness[98] (Figure 2). Zhu and his team engineered and manufactured hybrid iridium-ruthenium nanoenzymes (IrRuOxNPs) that sequentially utilize GSH via a redox electron pair self-cycling mechanism, facilitating Fenton-like reactions to produce a ROS storm. The findings demonstrated that IrRuOxNPs may efficiently inhibit and eradicate both Gram-positive and Gram-negative bacteria in vitro, establishing them as promising broad-spectrum antibiotics.[99]

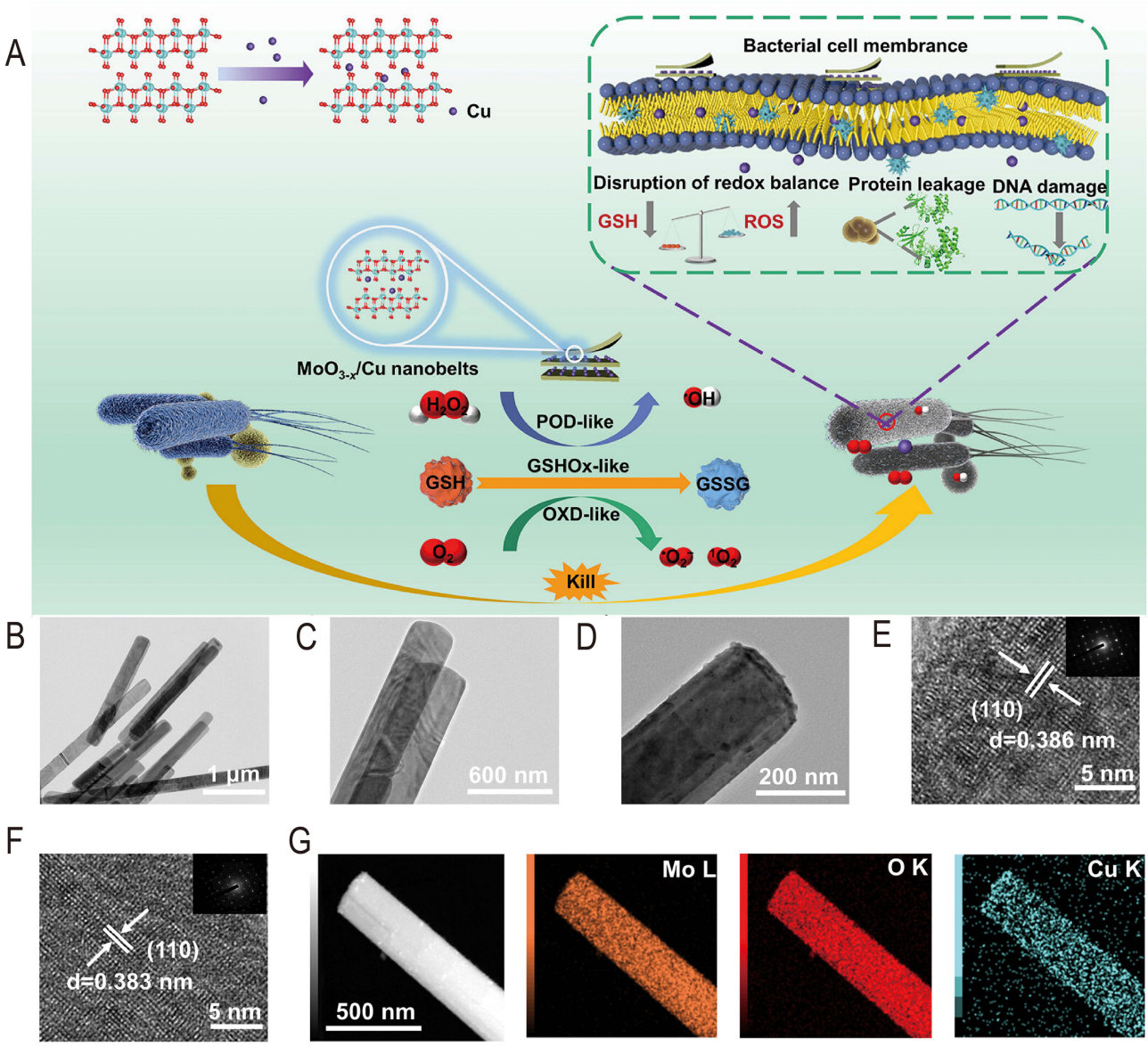


Figure 2 (**A**) MoO3–x/Cu Nanobelts Antibacterial Mechanism. (**B** and **C**) TEM images of MoO3 nanobelts. (**D**) TEM images of MoO3–x/Cu nanobelts. (**E**) MoO3 and (**F**) MoO3–x/Cu nanobelts HR-TEM images and SAED patterns. (**G**) EDS elemental mapping of MoO3–x/Cu. Reprinted from Liu H, Zuo Y, Lv S, et al. Ultralow loading copper-intercalated MoO(3) nanobelts with high activity against antibiotic-resistant bacteria. *ACS Appl Mater Interfaces*. 2024;16(14):17182–17192. Copyright © 2024 American Chemical Society.[98]

Non-ROS Dependent Mechanisms

Nonetheless, the quantity and rate of ROS and their associated products are not entirely manageable, and an excess of ROS Glutathione peroxidase on normal cells.[100] Consequently, it is imperative to investigate and devise a range of broad-spectrum sterilizing techniques that do not depend on ROS.

Some nanoenzymes can kill bacteria by directly contacting cells, thereby disrupting cellular structures. C-dots have demonstrated efficacy in diminishing biofilm development by inhibiting bacterial adhesion, interrupting quorum sensing, and eradicating bacteria, positioning them as a possible candidate for next-generation antibacterial therapies.[101] Dai and his team successfully developed ultra-small C-dots loaded with zinc single-atom nanoenzymes (Zn/C-dots), where zinc synergistically enhances the antibacterial activity of the C-dots, achieving over 90% antibacterial efficacy at a concentration of 100 μg/mL.[102] Silver nanoparticles (Ag NPs) can act as ROS scavengers, helping to regulate ROS levels during the wound healing process. Additionally, they exert antibacterial effects by disrupting bacterial cell membrane proteins and interacting with DNA. Liu and his team created hollow Ag@Pt-Au nanoparticles with a metal

substitution approach, wherein silver nanoparticles act as transporters, enabling a nanase cascade reaction that targets both gold and platinum, thereby successfully limiting bacterial proliferation.[103]

Nanoenzymes can also capture specific bacterial morphologies through physical recognition methods, enhancing their antibacterial performance by increasing the material's adhesion properties and surface area. Jing et al designed a morphology-based bioorthogonal catalytic nanoenzyme with antibacterial activity. They created a shell on the surface of the bacteria according to their shape, and then separated the bacteria from the shell through calcination, resulting in the designed bioorthogonal catalytic nanoenzyme. This nanoenzyme can selectively recognize corresponding pathogenic bacterial templates. As a bioorthogonal catalyst, the nanoenzyme can in situ catalyze the conversion of precursors into active antibacterial molecules, functioning as an effective bactericide. They applied this nanoenzyme to treat infections caused by S. aureus and E. coli in vivo. However, since the recognition is shape-based, distinguishing between bacteria of the same shape or different subtypes remains a significant challenge[104] (Figure 3). Future Research May Incorporate Promising Bacterial Recognition Methods, Such as Multimodal Recognition Systems, Shape-Morphing Materials, and Genetic Feature Targeting, to Address Current Limitations.

Some strategies involve designing rough surface structures to improve the adhesion of materials to bacteria, thereby increasing bacterial capture rates. Rough surface engineering is widely acknowledged as an effective method for improving bacterial adherence on nanoenzymes. Bacteria, adorned with many pili and flagella, can be readily trapped by coarse nanoscale structures, whereas normal cells are not drawn to them.[105] Moreover, the rough surfaces allow for a greater surface area and more edge defect active sites on the nanoenzyme surfaces, which enhances their intrinsic catalytic activity.[106–108] Significant work has been done to develop rough-surfaced nanoenzymes by fabricating defect-rich MoS_2 nanosheets on the surfaces of one-dimensional Cu nanowires (R-CM),[106] two-dimensional reduced graphene oxide (rGO) (MoS_2/rGO VHS),[107] and zero-dimensional Fe_3O_4 nanoparticles (Fe_3O_4@MoS_2-Ag),[108] resulting in greatly improved bacterial capture rates.

Xu et al reported a rough-surfaced carbon-iron oxide hybrid nanoenzyme (RCF) that enhances bacterial adhesion, thereby facilitating the catalysis of wound infections[109] (Figure 4). Engineered urchin-like PdCu nanoparticles can create relatively rough surfaces, hence augmenting the bacterial adhesion properties of nanoenzymes and resulting in enhanced antibacterial efficacy.[110]

Another strategy involves simulating the branched pseudopodia of human immune cells to increase the surface area for contact between materials and bacteria, thereby improving bacterial capture rates. Inspired by the mechanism by which neutrophils in the human immune system capture bacteria using branched pseudopodia, Qu's team created a MOF@COF nanoenzyme featuring pseudopodia-like surfaces and tailored microenvironments. The spiky COF provides multivalent topological interactions, allowing the nanoenzymes to strongly capture bacteria.[111]

Reducing the Impact of Glucose and Its Related Products

Local glucose accumulation caused by hyperglycemia is one of the most significant features of diabetic foot. Such accumulation can easily lead to infections and hinder vascular production and wound healing, making it crucial to reduce local glucose and related products. Currently, several studies have focused on directly adding glucose oxidase to lower local blood sugar levels.[23,112] However, the instability and difficult preparation of natural enzymes greatly limit their development. The emergence of nanoenzymes offers a solution to further enhance glucose oxidation efficiency.

Simulation of Glucose Oxidase

Some nanoenzymes can mimic glucose oxidase to regulate localized hyperglycemic environments. Throughout the past few years, gold nanoparticles exhibiting glucose oxidase(GOx) activity have emerged as a focal point of research, mitigating the limitations of natural GOx, including inadequate stability and elevated production costs.[113] Peng and his team synthesized hollow mesoporous organic tantalum nanospheres modified with dual nanoenzymes of Au and Pt, illustrating that these nanospheres can act as nanoenzymes that resemble glucose oxidase, especially catalyzing the oxidation of β-D-glucose to gluconic acid.[114] Additionally, Qi and his team developed a novel iron SAE (FeSAE@Au) modified with Au nanoparticles (AuNPs) for self-cascading catalytic reactions. In this dual nanoenzyme system, the embedded AuNPs act as a GOx mimic, catalyzing cellular glucose in situ and further enhancing the catalytic performance

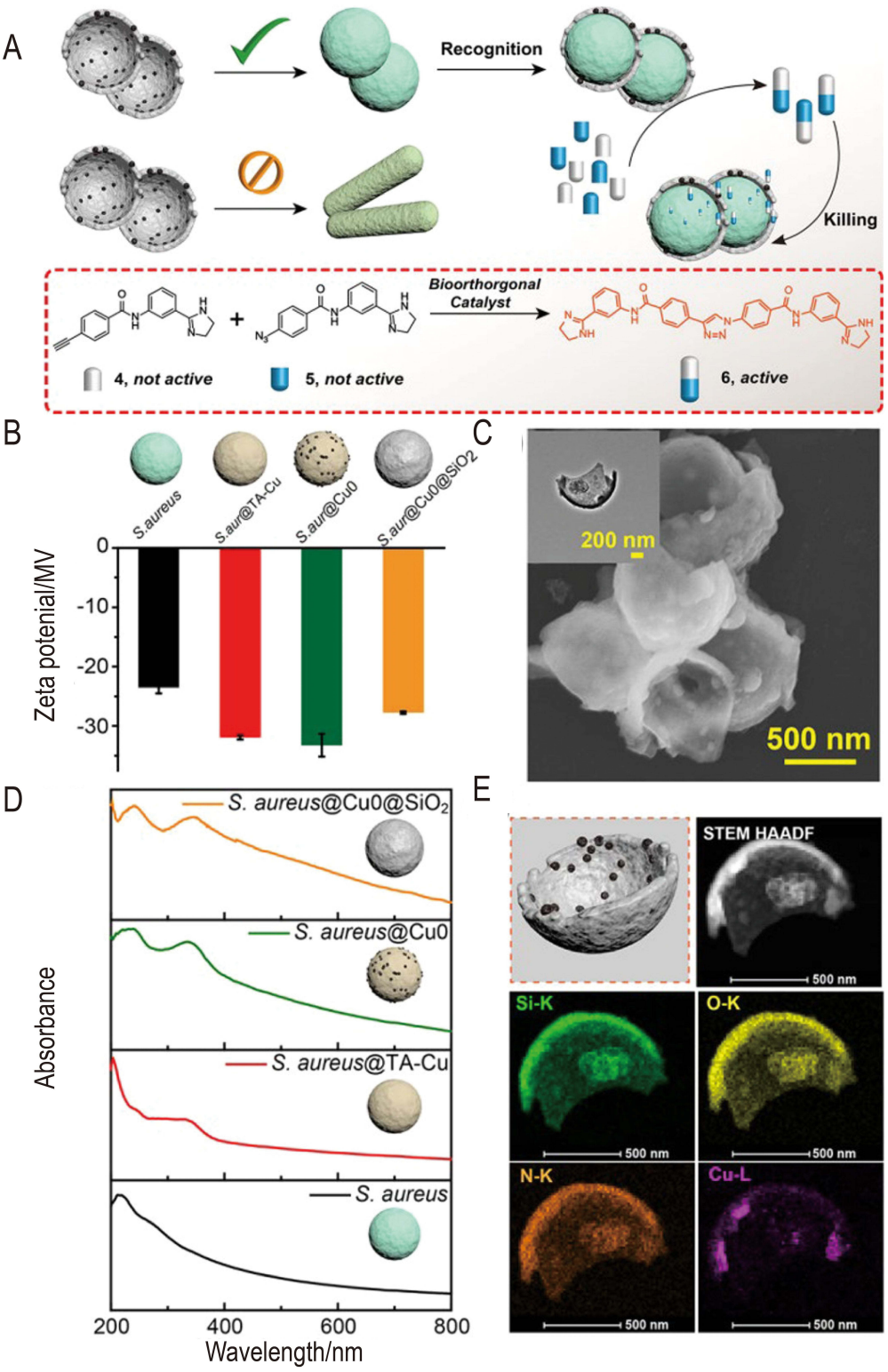


Figure 3 The schematic diagram of the bactericidal action of the antibody bioorthogonal catalytic nanoenzyme S-Ab and its successful construction is as follows. (**A**) The physical recognition bactericidal mechanism illustrates that the bioorthogonal catalytic nanoenzyme obtained through calcination possesses a specific morphology, enabling it to engage in selective binding with target bacteria. (**B**) Zeta potentials of S. aureus, S aureus@TA-Cu, S aureus@Cu0, and S. aureus@Cu0@SiO2,The metal ion-tannic acid (TA) system can be used for coordination and assembly on the surfaces of materials with different shapes or even at pore interfaces, where "@" denotes a coating of Cu-TA. (**C**) The SEM image of the half-shell antibody fragment catalyst S-Ab generated by ultrasonic treatment. Inset: TEM image of S-Ab. (**D**) UV–vis spectra of S. aureus, S aureus@TA-Cu, S aureus@Cu0, and S. aureus@Cu0@SiO2 solution. (**E**) The schematic diagram of S-Ab, the dark field TEM image of S-Ab, and the corresponding elemental mapping for Si-K, O-K, N-K, and Cu-L signals. Reprinted from Niu J, Wang L, Cui T, et al. Antibody mimics as bio-orthogonal catalysts for highly selective bacterial recognition and antimicrobial therapy. *ACS Nano*. 2021;15 (10):15841–15849. Copyright © 2021 American Chemical Society.[104]

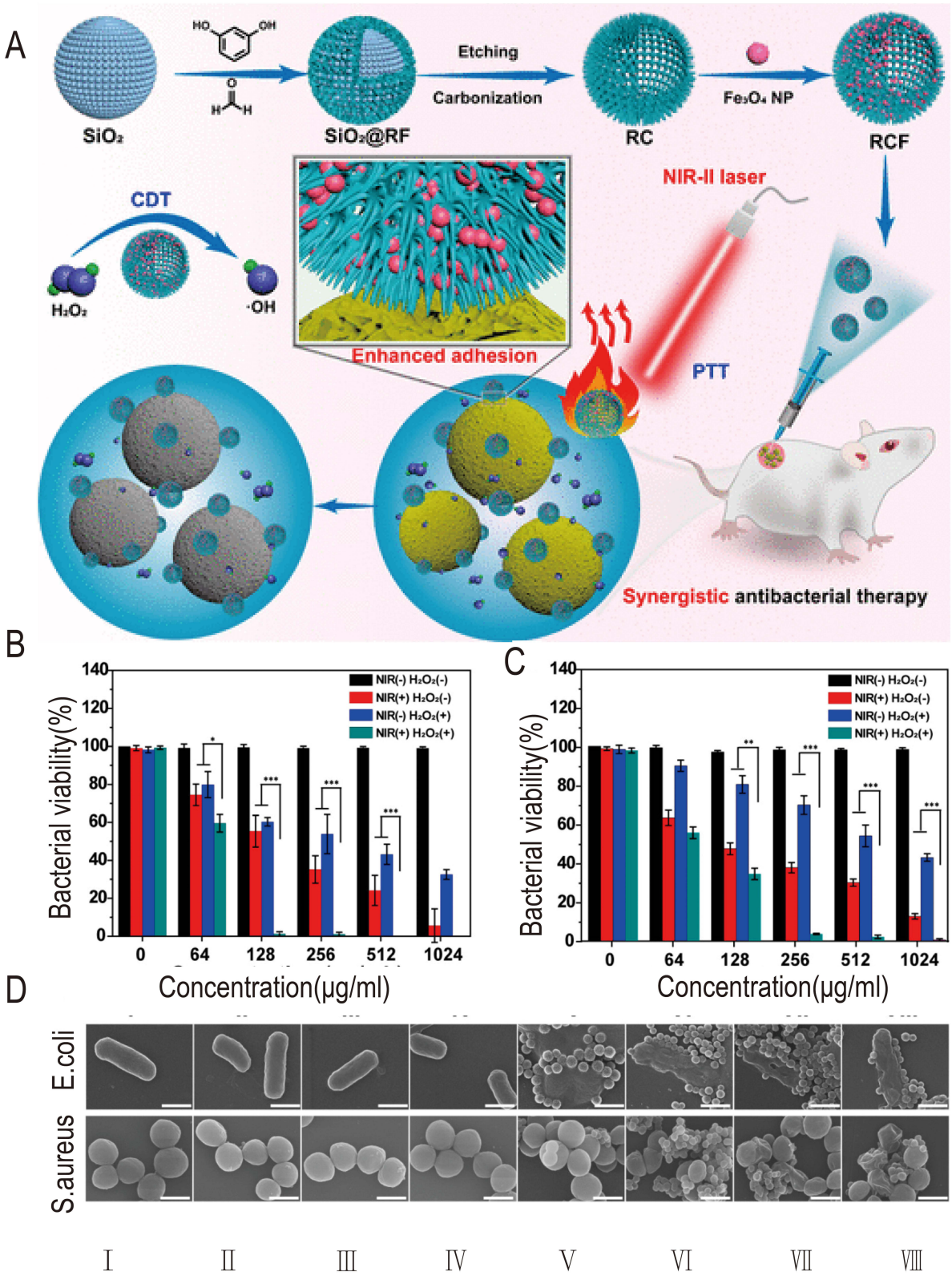


Figure 4 (**A**) Schematic diagram of the bactericidal action of RCF. (**B** and **C**) Show the bacterial survival rates of Escherichia coli and Staphylococcus aureus in different groups after RCF treatment, determined by the plate counting method. (**D**) SEM images of Escherichia coli and Staphylococcus aureus after different treatments: (I) PBS, (II) H_2O_2, (III) NIR, (IV) H_2O_2 + NIR, (V) RCF, (VI) RCF + H_2O_2, (VII) RCF + NIR, and (VIII) RCF + RH_2O_2 + NNR. Scale bar: 1 μm. *p <0.05, **p<0.01, ***p< 0.001. Reprinted from Liu Z, Zhao X, Yu B, Zhao N, Zhang C, Xu F-J. Rough carbon-iron oxide nanohybrids for near-infrared-II light-responsive synergistic antibacterial therapy. *Acs Nano*. 2021;15(4):7482–7490. Copyright © 2021 American Chemical Society.[109]

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of FeSAE with glucose oxidase-like activity.[115] Bimetallic nanoenzymes with core/shell or alloy architectures demonstrate superior catalytic activity compared to their monometallic counterparts, attributable to the interactions among several metals that influence the distribution of d-band electrons. Tang and his team synthesized bimetallic AuPd nanoenzymes with a dumbbell structure by mediating the growth of nano-Pd onto the ends of Au nanorods. This design further enhanced the catalytic efficiency of the glucose oxidase-mimicking nanoenzymes.[116]

The distinctive architecture of certain nanozymes can offer superior active sites for glucose oxidase (GOx), significantly augmenting its catalytic efficacy, including Ti_3C_2 nanosheets, nitrogen-doped carbon nanomaterials, and black phosphorus quantum dots. For instance, Xu and his team modified GOx onto nitrogen-doped carbon (NC) nanoparticles, forming biomimetic nanoenzymes (NC@GOx NPs)[117] (Figure 5). Liang and his team loaded GOx onto the surface of two-dimensional Ti_3C_2-MXene,[118] while Mei and his team assembled GOx onto CoFe layered double hydroxide (CoFe-LDHs) monolayer nanosheets.[119] These combinations of oxidases with nanomaterials have effectively improved glucose oxidation efficiency.

Recent studies indicate that iron-carbon nanoparticles can further enhance the catalytic efficiency of GOx. Zhang and his team synthesized iron-carbon nanoparticles (MF1-3) exhibiting sizes from 13.7 to 27.6 nm and shell thicknesses varying between 1 to 5 nm through a high-temperature arc method. Among these, MF3, functioning as a magnetic core composite nanoparticle, demonstrated optimal catalytic activity.[120]

Additionally, the reaction of catalyzing glucose decomposition requires the participation of oxygen, prompting some studies to enhance oxidation efficiency by ensuring sufficient oxygen supply. He and his team designed a multifunctional nanoenzyme Co/La-PB@MOF-199/GOx. This composite nanoenzyme compensates for oxygen consumption through its peroxidase-like (CAT) properties, allowing for sustained glucose consumption.[121] Details on nanoenzymes that improve local oxygen content will be discussed in section 3.2.3.

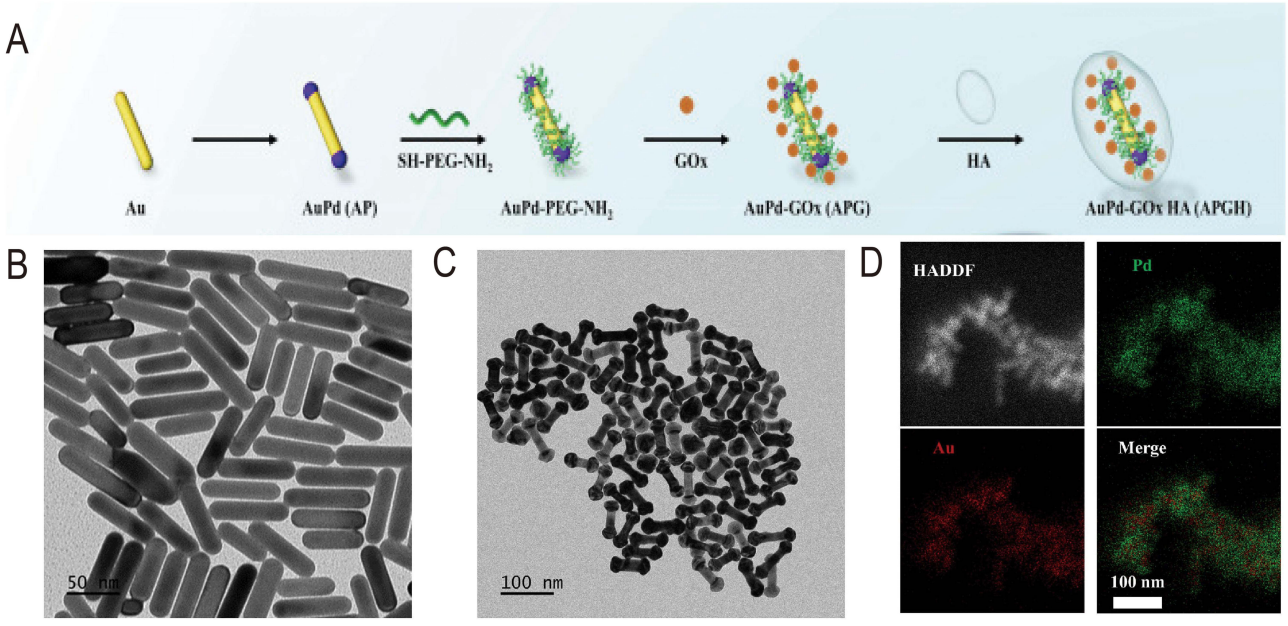

Figure 5 (**A**) Schematic diagram of the synthesis of AuPd nanoenzymes and composite nanomaterials (APGH), which enhances the water solubility of the nanoenzymes, making them suitable for biological environments. (**B** and **C**) are respectively electron microscopy images of Au nanorods (NRs) and AuPd nanoparticles (NPs). (**D**) XRD spectrum of AuPd NPs, where the X-ray powder diffraction results confirm the presence of Au and Pd in the bimetallic nanostructure. Reprinted from *Acta Biomater.* Volume 177. Tang Z, Hou Y, Huang S, et al. Dumbbell-shaped bimetallic AuPd nanoenzymes for NIR-II cascade catalysis-photothermal synergistic therapy. 431–443, Copyright 2024, with permission from Elsevier.[116]

Mitigation of the Effects of Glycation Products

Advanced glycation end products (AGEs) are formed from excess sugars and proteins through the Maillard reaction, which can further disrupt immune balance and impede wound healing.[122] Recent studies indicate that nanoenzymes can mitigate the damage caused by high-sugar environments to cells and tissues in various ways.

One strategy focuses on preventing the glycation of AGEs. Cutting-edge research shows that CeO_2 nanoenzymes can inhibit the glycation and cross-linking of α-crystallin, acting as anti-glycation agents.[123] Cheng and his team innovatively introduced unique anti-glycation cerium oxide nanorods into self-healing, erasable hydrogels, accelerating hemostasis and reducing AGEs to remodel the wound microenvironment, thereby promoting diabetic wound healing.[124]

Moreover, since AGEs can hinder wound healing processes by inhibiting the expression of nitric oxide (NO) synthase in endothelial cells, another strategy emphasizes alleviating the negative effects of AGEs on wounds by supplementing exogenous NO. Yang and his team successfully loaded S-nitrosoglutathione (GSNO) nanoparticles into hydrogels, effectively reducing local AGE levels and lowering oxidative stress, significantly improving wound healing in diabetic rats. This targeted delivery approach designed to mitigate the harmful effects of AGEs presents significant clinical promise for the management of diabetic wounds[125] (Figure 6A–C).

Antioxidant

In the human body, natural antioxidant enzyme systems exist, such as superoxide dismutase (SOD), Catalase (CAT), and Glutathione peroxidase(Gpx).[126] These enzymes contain metal elements; for example, SOD1 includes Zn/Cu, while SOD2 contains Mn.[127] They catalyze the degradation of ROS through valence state conversion, providing cellular protection. Nanoenzymes can also catalyze the degradation of ROS through various mechanisms. The application of nanoenzymes for the removal of excess ROS in diabetic wounds presents a promising strategy for mitigating wound inflammation and enhancing healing rates.

Firstly, nanoenzymes can mimic different antioxidant enzyme activities by altering the arrangement of the same atoms. CAT is an enzyme that catalyzes the decomposition of hydrogen peroxide into water and oxygen. In diabetic wounds, it can remove hydroxyl radicals through redox reactions, thereby mitigating local oxidative damage and inflammation. An optimal therapeutic CAT mimetic ought to promote efficient H_2O_2 dismutation while concurrently reducing the generation of HO• radicals. Ning's team reported a series of salt-alkali-based manganese (Mn(III))

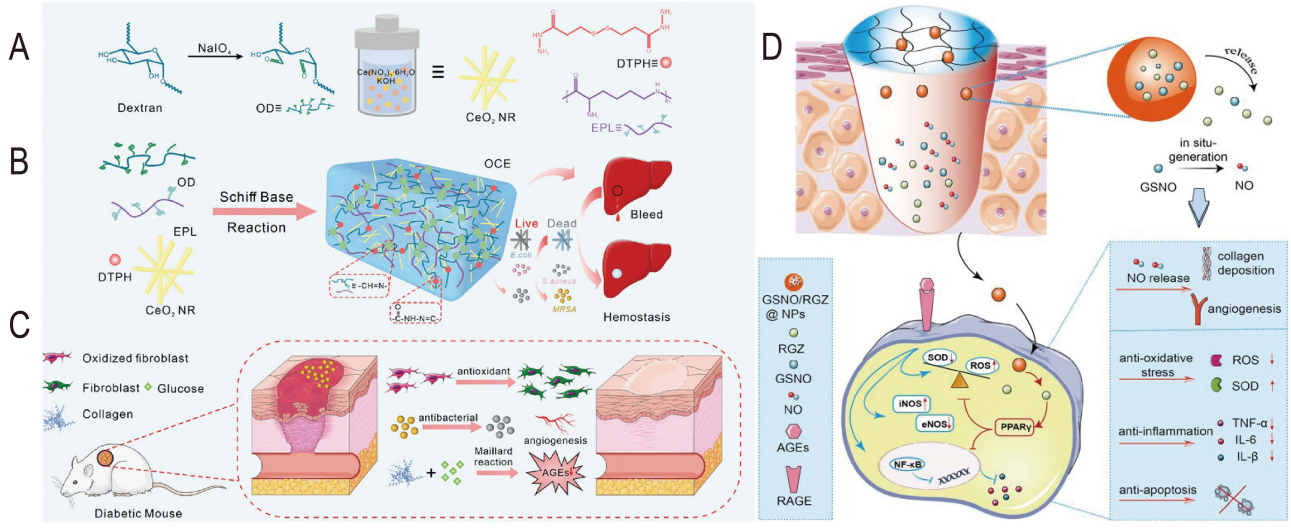

Figure 6 (**A**) Synthesis of oxidized dextran (OD) and CeO_2. (**B**) Preparation of OCE hydrogel. (**C**) Application of OCE hydrogel in the repair of MDR-infected diabetic wounds. Reprinted from Cheng F, Wang S, Zheng H, et al. Ceria nanoenzyme-based hydrogel with antiglycative and antioxidative performance for infected diabetic wound healing. *Small Methods*. 2022;6(11):e2200949. © 2022 Wiley-VCH GmbH.[124] (**D**) Schematic diagram of the NPs/hydrogel local co-delivery system. The co-delivery system reverses the harmful effects induced by AGEs through local supplementation of NO and intracellular delivery of rosiglitazone (RGZ). Reprinted from Yang Y, Huang S, Ma Q, et al. Combined therapeutic strategy based on blocking the deleterious effects of AGEs for accelerating diabetic wound healing. *Regen Biomater*. 2024:11:rbae062. Creative Commons.[125]

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metallacapsules that function as mimics of catalase. In these metallacapsules, three Mn centers are positioned very closely together, forming unique "active site" cage-like molecules. This arrangement greatly enhances metal cooperativity, enabling effective dismutation of H_2O_2 while minimizing HO• production. The triamine (Salen) manganese complex can initially simulate the dinuclear nature of the natural CAT active site, showing about a sevenfold enhancement in catalytic activity compared to the monomeric Mn(Salen) control, while reducing HO• formation by approximately 50 times[128] (Figure 6D).

Secondly, modifying the surface functional groups of nanoenzymes can endow them with catalytic activities similar to natural enzymes. Carbon dots (C-dots) have attracted considerable study attention in biomedicine owing to their diminutive size, facile synthesis, economical nature, and favorable biocompatibility. The dimensions of C-dots and the prevalence of active sites confer enzyme-like catalytic properties. Current studies have explored the mechanisms underlying the SOD-like activity of C-dot nanoenzymes through surface modifications, revealing that the SOD-like activity of C-dots depends on their surface functional groups, including hydroxyl, carboxyl, and amino groups. Liu's team has confirmed that C-dot nanoenzymes can effectively enter cells, eliminate harmful ROS, and protect cells from oxidative damage.[129]

Thirdly, nanoenzymes with multiple valence states can exhibit different enzyme-like activities through conversions between their various oxidation states. Cerium nanoparticles (CeNPs) are a type of nanoenzyme that are structurally stable and possess sustained radical scavenging activity under physiological conditions. Due to their dual oxidation states, CeNPs exhibit significant antioxidant and catalytic properties: nanoparticles with a higher Ce^{3+}/Ce^{4+} ratio display superoxide dismutase (SOD)-mimicking activity, while those with a lower ratio enhance catalase (CAT) activity. Both SOD and CAT contribute to antioxidant defense in vivo. In addition to the Ce^{3+}/Ce^{4+} ratio, factors such as nanoparticle size, solution environment, and pH can also influence nanoenzyme activity.[130] Zhang's team established the LA-PEG-CeNPs system by modifying CeNPs with lipoic acid (LA) and polyethylene glycol (PEG).[131] Meanwhile, Jiang's team endowed Ce-MBGNs with antioxidant nanoenzyme characteristics through the conversion between Ce(III) and Ce(IV) to scavenge ROS generated by diabetes.[132]

Furthermore, Nanoenzymes can directly engage in redox processes and function as co-factors that improve catalytic efficiency by stabilizing the spatial conformation of antioxidant enzymes. Research suggests that magnesium ions function as co-factors, facilitating the catalytic activity of other active metal ions and so augmenting their efficacy as antioxidant enzymes. The electronic transfer between the two markedly enhances the velocity of redox reactions.[133] Pu's team incorporated magnesium ion-doped molybdenum-based polymetallic oxides (Mg-POM), a novel bioactive nanoenzyme, into GelMA hydrogels. Experimental results demonstrated that this hydrogel exhibits excellent ROS scavenging capabilities, significantly improving the inflammatory microenvironment.[134]

Lastly, recent studies increasingly demonstrate that dual catalysis involving two or more nanoenzymes can rearrange surface electrons, significantly enhancing catalytic activity. Carbon compounds are extensively utilized as optimal supports for single-atom catalysis owing to their distinctive structure and steady physicochemical characteristics. When carbon materials function as supports, surface single atoms can affect the local electronic structure of the support, creating robust metal-support interactions that modify the spatial state and energy distribution of adsorbates, so improving the catalyst's performance. Additionally, the large surface area and abundant anchoring sites of C-dots provide excellent support for the attachment of single-atom nanoenzymes (SANs). Together, they form a dual catalysis system that exhibits increased enzymatic activity. Dai's research shows that zinc single-atom nanoenzymes (Zn/C-dots) loaded on ultra-small C-dots can effectively enter cells, accumulate in mitochondria, and remove excess ROS. Compared to C-dots alone, Zn/C-dots also promote endothelial cell migration and new blood vessel formation.[102]

Improving Cellular Hypoxia

Oxygen levels are a vital indicator of wound healing, impacting the process through multiple processes which include avoiding wound infection, increasing cell proliferation, initiating angiogenesis, and decreasing inflammation. Presently, topical oxygen therapy and hyperbaric oxygen therapy are employed clinically to manage diabetes.[135,136] Nonetheless, these technologies do not resolve challenges such as inadequate tissue permeability and the complexities of delivering and sustaining sufficient oxygen levels, leading to subpar therapy results.[137] Nowadays, nanoenzymes and their analogs

have demonstrated considerable potential in expediting wound healing. Nanozymes primarily generate oxygen at the wound site through endogenous and exogenous pathways, thereby improving the diabetic microenvironment.

Decomposition of Endogenous Substances

From an endogenous standpoint, the surplus H_2O_2 in the wound microenvironment offers ample substrates for O_2 generation, thus the specific and efficient decomposition of H_2O_2 in this milieu has emerged as a prominent research focus. Certain studies concentrate on augmenting the activity of individual metal oxidases to facilitate localized oxygen supplementation. Du and his team applied a MnO_2 coating on the surface of two-dimensional black phosphorus nanosheets, effectively catalyzing the endogenous H_2O_2 to yield oxygen.[113] Wang and his team have created an innovative composite nanoenzyme comprising mesoporous silica and nano-ceria, demonstrating commendable peroxidase activity and efficiently converting elevated concentrations of H_2O_2 into O_2.[138]

Several studies integrate two or more metal nanoparticles to mitigate the impact of variables like acidic pH and hypoxic environments on nanomaterial activity, hence augmenting their catalytic efficiency. Dong and his team ingeniously amalgamated copper, manganese, and sulfur nanoparticles to synthesize an innovative pH-responsive nanoenzyme (PCMS NPs). Experimental findings indicated that under acidic circumstances, PCMS nanoparticles had peroxidase-like and catalase-like activities, converting H_2O_2 into O_2.[139] Li and his team created a light-responsive nanozyme hydrogel, wherein the central Fenton-like reaction involves a heterostructure made of SnO_2 and Cu_2O. Thereafter, the core was enveloped with the light-responsive material polydopamine (PDA) to produce Cu_2O-SnO_2-PDA (PCS), enabling the modulation of reaction intensity by external light intensity.[140] Kim and his team synthesized manganese ferrite nanoparticles, and studies revealed that these composite nanoparticles can perpetually generate oxygen in hydrogen peroxide-rich hypoxic conditions while downregulating hypoxia markers such as HIF-1α.[13]

However, during Fenton reactions, the inevitable production of a certain amount of ROS can lead to varying degrees of cellular damage. Therefore, it becomes crucial to reduce the generation of ROS while producing O_2. The development and utilization of cerium-containing nanoenzymes provide a viable solution to this issue. Ce-UiO-66 is a cerium-based metal-organic framework with ROS scavenging properties. Ce-UiO-66 possesses abundant Ce(III)/Ce(IV) coupling sites, capable of generating oxygen from H_2O_2, exhibiting CAT activity. The multi-cavity structure of Ce-UiO-66 can generate electron holes, and its porous channels can function as micro-reactors, further enhancing its ROS scavenging capability.[141] Wang and his team proposed a comprehensive adaptive photodynamic therapy (PDT) antioxidant model to actively regulate ROS balance. They designed a gelatin-hyaluronic acid hydrogel (Gel-HA-Se@CeO_2NPs) embedded with selenium-modified cerium oxide nanoparticles (Se@CeO_2NPs). These nanoparticles serve both as nanoenzymes and as photosensitizers (PS). As nanoenzymes, they exhibit peroxidase and superoxide dismutase activities, converting hydrogen peroxide and superoxide anions into oxygen. As a PS, they cooperate with oxygen under near-infrared (NIR) irradiation to rapidly generate singlet oxygen, which serves a bactericidal function for infected wounds[142] (Figure 7).

Arginine (Arg) is a critical mediator in the wound healing process. In the early stages of healing, it is primarily produced by inducible NO synthase in M1 macrophages, catalyzing the generation of NO from hydrogen peroxide (H_2O_2). In the later stages, arginase from M2 macrophages catalyzes the production of ornithine, promoting tissue repair.[143] Yang and his team designed an arginine-loaded nanoenzyme (FTA) that mimics peroxidase activity. FTA can locally remove excess ROS from the wound site and convert them into oxygen to alleviate hypoxia. Simultaneously, arginine is released and metabolized by NO synthase in M1 macrophages to facilitate early vascular repair.[144]

Mitochondria are crucial sites for oxygen consumption and ROS production in organisms. Oxidative damage to mitochondria can lead to the inactivation of related oxidases, resulting in local tissue hypoxia. Some nanoenzymes can alleviate hypoxia by repairing mitochondrial oxidative damage. He and his team engineered a zeolitic imidazolate framework encapsulated with cerium dioxide, which incorporates the Rho-associated protein kinase inhibitor Y-27632. CeO_2 demonstrates superoxide dismutase and catalase capabilities, efficiently eliminating excess reactive oxygen species to mitigate mitochondrial damage. Y-27632 can restore impaired mitochondrial DNA, enhancing endothelial cell proliferation. Endothelial cells internalize CeO_2-Y@ZIF-8 nanoparticles, which facilitate the degradation of peroxides into water and oxygen within the cytoplasm and mitochondria, thereby supplying oxygen to the cells, while concurrently

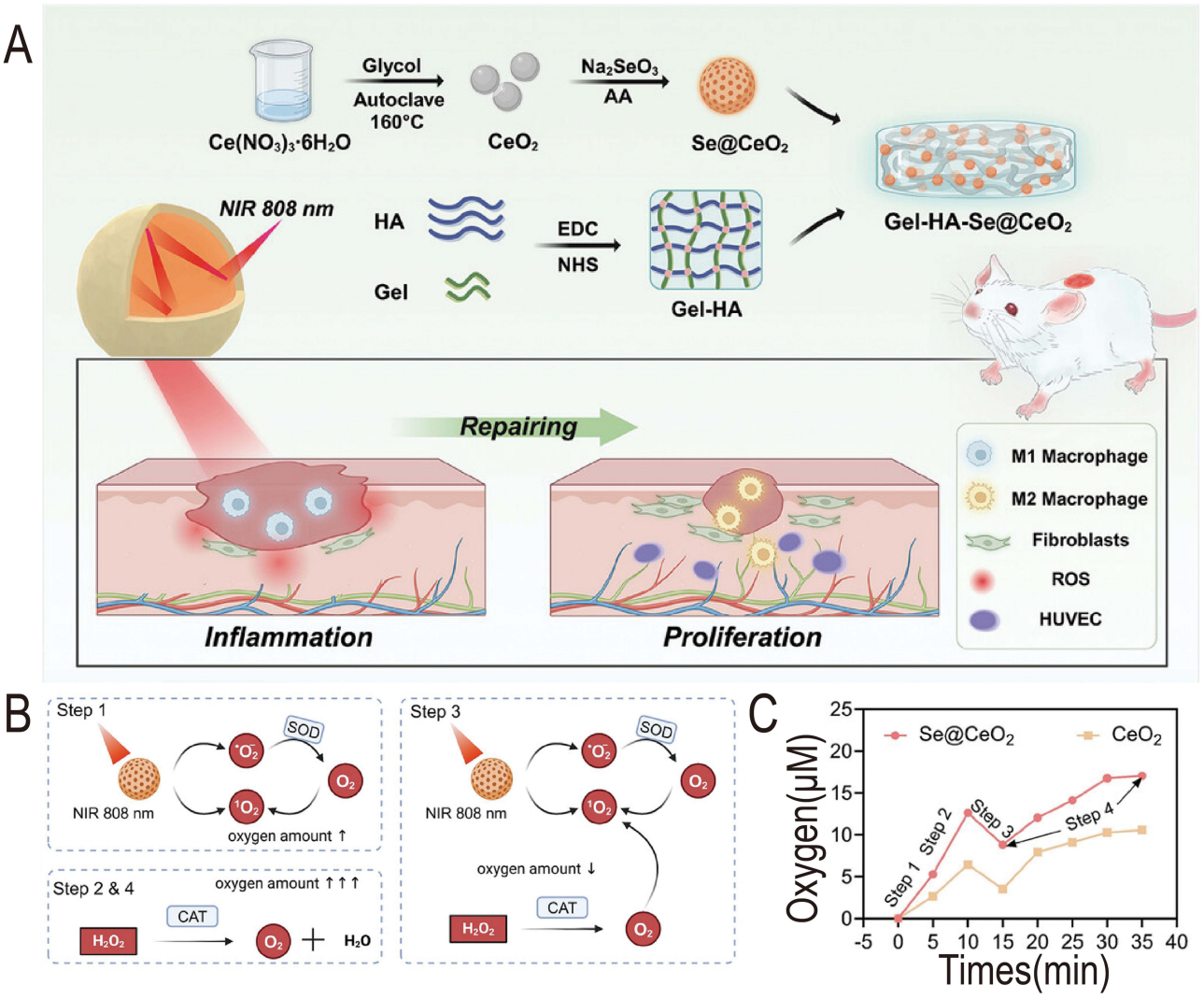

Figure 7 (**A**) Applications and Potential Mechanisms of Gel-HA-Se@CeO_2 Hydrogel in Promoting Wound Healing through Controllable PDT. (**B**) Working Diagram of the ROS Balance System (**C**) Corresponding oxygen release curves of CeO2 and Se@CeO2. Reprinted from Wang M, Liu Y, Yang S, et al. Collaboration in contradiction: self-adaptive synergistic ROS Generation and scavenge balancing strategies used for the infected wounds treatment. *Adv Healthc Mater.* 2024;14:e2402579. © 2024 Wiley-VCH GmbH.[142]

inhibiting the NLRP3 inflammasome pathway. This mitigates oxidative damage to mitochondrial DNA, providing a more durable remedy for tissue hypoxia.[145]

Transport of Exogenous Oxygen

In addition, numerous nanoparticles can proficiently transport exogenous oxygen by incorporating it into the relevant tissues and cells. Hydrogen peroxide can serve independently as a source of oxygen release. Nevertheless, owing to its cytotoxicity, it necessitates encapsulation within microcapsules followed by quick decomposition. Catalase is employed as a catalyst to expedite the transformation of hydrogen peroxide into water and oxygen.[146] For example, Abdi and associates contained hydrogen peroxide within a core composed of poly(D,L-lactide-co-glycolide). The inner layer was subsequently encased within a sodium alginate film. Catalase was affixed to the alginate in the second layer to accelerate the breakdown process of hydrogen peroxide as it penetrates this layer.[147] Mollajavadi and his team developed a novel bio-scaffold material using 4% (w/v) sodium alginate (Alg) as the primary material and calcium peroxide as the oxygen-releasing agent. It can interact with water, resulting in the release of oxygen, which alleviates hypoxia and facilitates the efficient distribution of oxygen inside the scaffold.[148]

Regulation of Cellular Functions

Macrophages

The immune regulatory imbalance in diabetic wounds is marked by an elevation of pro-inflammatory (M1) macrophages and a reduction of anti-inflammatory (M2) macrophages, with M1 macrophages constituting almost 80% of the cells at the periphery of chronic wounds. This disparity results in sustained inflammation.[149,150] Therefore, regulating macrophage polarization is crucial for achieving effective healing in diabetic wounds. Additionally, macrophage-mediated phagocytosis and autophagy can influence the local inflammatory state.[151,152] The rapid development of nanomaterials provides several solutions for the immunomodulation of macrophages in the wound microenvironment.

Achieving Phenotype Transformation

ROS are strong inducers of the inflammatory response in macrophages, promoting M1 polarization through specific pathways. Most strategies aim to facilitate the transformation from M1 to M2 phenotypes by either removing ROS or improving the hypoxic conditions of the microenvironment. Pu and his team integrated magnesium ion-doped molybdenum-based polyoxometalates (Mg-POM) into GelMA hydrogels, creating a nanoenzyme-functionalized hydrogel. Through the application of ultraviolet light irradiation, they accomplished cross-linking, yielding a hydrogel characterized by a consistent, porous three-dimensional network structure. In vitro investigations demonstrated that this hydrogel effectively scavenged reactive oxygen species (ROS), enhanced the inflammatory milieu, and facilitated macrophage reprogramming towards the M2 phenotype.[134]

In recent years, numerous studies have further elucidated the mechanisms of macrophage phenotypic transformation. Guo and his team synthesized bovine serum albumin-bilirubin-platinum nanoparticles (BSA-BR-Pt NPs) that possess synergistic properties for alleviating hypoxia and clearing ROS. Platinum works in conjunction with bilirubin to eliminate ROS while simultaneously generating oxygen. Hypoxia-inducible factor (HIF) is a key regulator of oxygen homeostasis. Experimental results demonstrated that BSA-BR-Pt NPs can inhibit the HIF-1α pathway, leading to a shift in glucose metabolism from glycolysis to oxidative phosphorylation, thereby promoting M2 polarization in macrophages.[153] Tian and his team developed a chondroitin sulfate (CS)-modified MoS_2 nanoenzyme that can modulate the M1/M2 polarization of macrophages by reducing the production of pro-inflammatory substances such as TNF-α, IL-1β, and IL-6.[154]

There are also strategies demonstrating that carbon monoxide (CO) gas can drive macrophages toward M2 polarization. Wu and his team constructed a multifunctional bioactive interface with antioxidant stress and immunomodulatory properties on titanium implants. Specifically, manganese dioxide nanosheets were coated on mesoporous polydopamine nanoparticles loaded with a CO gas precursor (MnO), resulting in 2-CO@MPDA NPs, which were then integrated into titanium implants to create MCM-Ti. The reactive release of CO gas mediated by the microenvironment effectively drives macrophages toward M2 polarization, thereby improving the inflammatory response. The potential mechanism involves CO gas upregulating the expression of heme oxygenase-1 (HO-1), further activating the Notch/Hes1/Stat3 signaling pathway[155] (Figure 8A–C).

Activation of Exocytosis

Cell proliferation and the reversal of inflammation in the wound microenvironment are downstream events of exocytosis. Nanomaterials can promote wound healing by activating macrophage exocytosis and inhibiting excessive inflammatory activation. The disturbance of homeostasis in the wound microenvironment, specifically the excessive activation of intracellular oxidative stress and absence of apoptotic signals, may inhibit macrophage exocytosis. Wang and his team introduced a biomimetic "apoptotic signal" integrated within a polydopamine-coated short fiber matrix. The "apoptotic signal" originated from cerium oxide (CeO_2) nanoenzymes enveloped in apoptotic neutrophil membranes, enhancing macrophage identification and the regulation of oxidative stress. Additionally, the short fiber "biomimetic matrix" was engineered to incorporate apoptotic signals via several adhesion sites via π-π stacking and hydrogen bonding interactions. An implanted nanoenzyme/short fiber matrix that mimics apoptosis was developed to combine apoptotic signals with a biomimetic matrix, with the objective of facilitating inflammation reversal and creating a pro-apoptotic microenvironment that supports efferent cell functions. In vitro and in vivo evidence indicated that the biomimetic short fibers in the

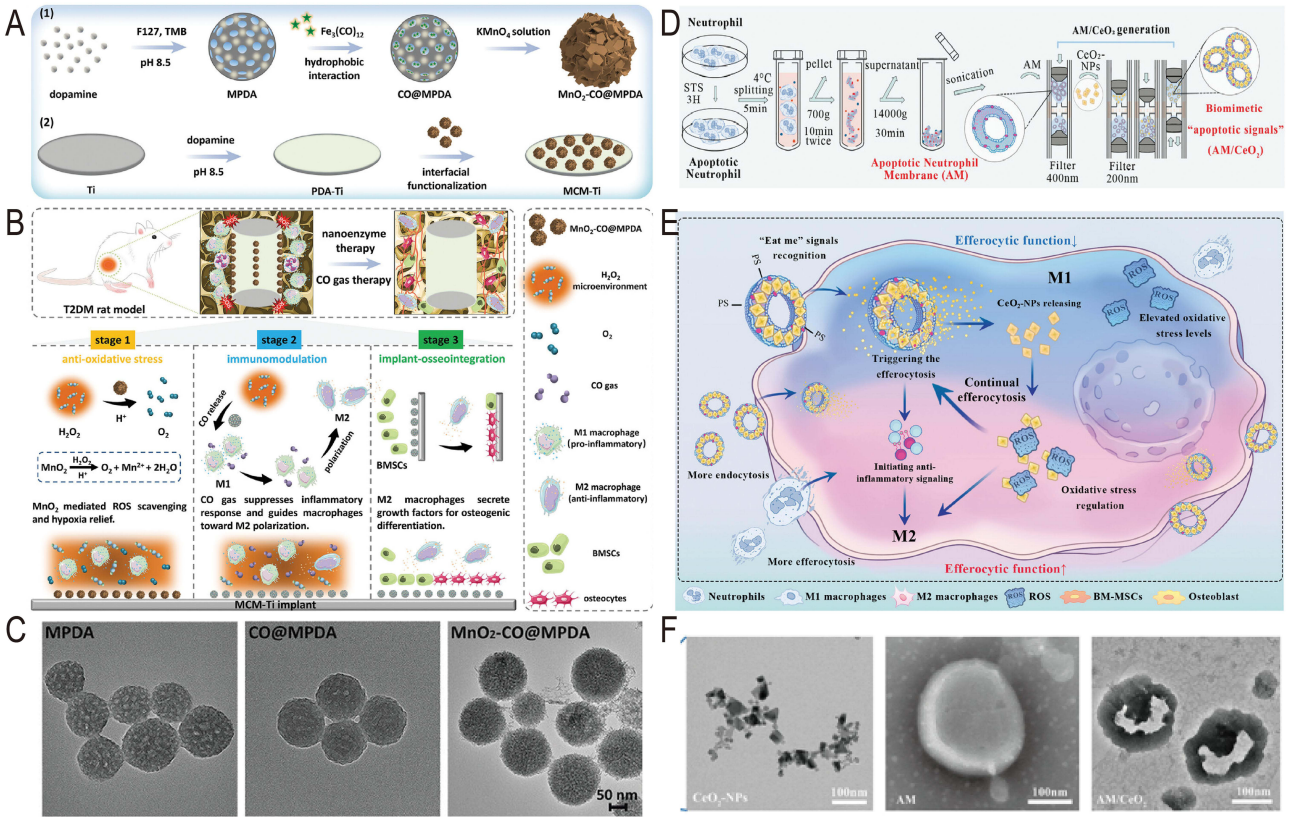

Figure 8 (**A**) Schematic Diagram of MnO_2-CO@MPDA NPs Fabrication. (**B**) Mechanism of Macrophage Phenotypic Transformation Mediated by CO. (**C**) TEM images of different nanoparticles (scale bar: 50 nm). Reprinted from Wu J, Chen M, Xiao Y, et al. The bioactive interface of titanium implant with both anti-oxidative stress and immunomodulatory properties for enhancing osseointegration under diabetic condition. *Adv Healthc Mater.* 2024;13:e2401974. © 2024 Wiley-VCH GmbH.[155](**D**) Schematic Diagram of AM/CeO_2 Construction. (**E**) Mechanism of Macrophage Phenotypic Transformation Induced by Apoptotic Signals Through Exocytosis. (**F**) Representative TEM images of CeO2-NPs, AM, and AM/CeO2. Reprinted from Wang H, Zhang Y, Zhang Y, et al. Activating macrophage continual efferocytosis via microenvironment biomimetic short fibers for reversing inflammation in bone repair. *Adv Mater.* 2024;36(30):e2402968. © 2024 Wiley-VCH GmbH.[156]

microenvironment might induce prolonged exocytosis in macrophages, thus mitigating excessive inflammatory activation[156] (Figure 8D–F).

Certain nanoenzymes modulate macrophage autophagy in a shape-dependent fashion, contributing to cellular homeostasis and mitigating local inflammation. Macrophage autophagy is an essential self-protective intracellular mechanism that sequesters damaged organelles and redundant proteins, facilitating their transfer to lysosomes for destruction. This repair and maintenance process is essential for maintaining cellular homeostasis and preventing inflammation and apoptosis. Zhou and his team reported that gold nanoparticles regulate autophagy in a shape-dependent manner, with nanospheres inducing greater accumulation of autophagosomes compared to nanorods.[157] Hu and his team designed and engineered a unique quadruped needle-like palladium-hydrogen nanoenzyme (denoted as TN-PdH) with ideal ROS scavenging capabilities. Both in vitro and in vivo findings validated the synergistic benefits among autophagy activation, anti-inflammation, and antioxidation.[158]

Fibroblasts

Fibroblasts are distinct spindle-shaped cells that are vital in the formation and remodeling of the extracellular matrix, rendering them indispensable in the wound healing process.[159] Promoting the survival and proliferation of fibroblasts in the wound microenvironment has emerged as a new direction for nanoenzyme therapies targeting chronic non-healing wounds.

Liu and his team developed iron-doped carbon dots (Fe-CDs) using a simple one-pot pyrolysis method, demonstrating superior photothermal conversion and light-augmented enzyme-like characteristics for synergistic antibacterial therapy and wound healing. Notably, the doping of iron endows the C-dots with enhanced peroxidase (POD)-like activity,

generating heat and ROS to kill both Gram-positive and Gram-negative bacteria. This study indicated that Fe-CDs enhance fibroblast proliferation, angiogenesis, and collagen deposition by inhibiting infection, hence greatly enhancing wound healing efficiency.[160]

Expanding upon prior investigations, Gu and his coworkers evaluated a cerium oxide nanoenzyme (at a concentration of 25 μg/mL) that markedly enhances human skin fibroblast proliferation and exhibits elevated superoxide dismutase activity. They incorporated this enzyme into GelMA hydrogels to create cerium oxide nanoenzyme-methyl methacrylate gelatin (GelMA) hydrogels.[161] Yan and his team successfully prepared gelatin-polyethylene glycol hydrogels loaded with silver nanoparticles (AgNPs). Their experiments showed that the proliferation activity of human fibroblasts (HFbs) cultured in soaking solutions of composite hydrogels at concentrations of 25.0 and 50.0 mg/mL was significantly increased.[162] Both studies further explored the quantitative effects of nanoenzymes on fibroblast proliferation.

Endothelial Cells

Nanoenzymes can promote the proliferation of endothelial cells by delivering VEGF or enhancing the secretion of factors associated with endothelial cells. VEGF is a crucial growth factor with significant pro-angiogenic activity, stimulating endothelial cell proliferation, providing anti-apoptotic effects, increasing vascular permeability, and promoting cell migration.[163] He and his team initially encapsulated VEGF within methylacrylated sulfonated chitosan (SCSMA) microspheres (V@MP), which were later incorporated into hyaluronic acid (HA) microneedles. The swift disintegration of HA retains the V@MP within the wound, facilitating the gradual degradation of SCSMA and prolonged release of VEGF, thus fostering angiogenesis. In vitro and in vivo investigations revealed that this biphasic drug release smart microneedle device promotes cell proliferation and migration, hence aiding angiogenesis and tissue regeneration.[164] Pu et al created a nanoenzyme-functionalized modulator of the regenerative microenvironment (AHAMA/CS-GOx@Zn-POM) for efficient diabetic wound healing. This innovative design combines aldehyde and methacrylic anhydride-modified hyaluronic acid hydrogel (AHAMA) with chitosan nanoparticles (CS NPs), encapsulating zinc-based polymetallic oxide acid nanoenzymes (Zn-POM) and GOx, enabling the prolonged release of both enzymes. It produces cytokines, including TGIF2, VEGF, and IGF-1, via paracrine actions, thereby facilitating angiogenesis and the regeneration of type I collagen. The sustained release of drugs can be attributed to the intrinsic physicochemical properties of the nanoenzyme. Experimental results demonstrated that by the 14th day, the nanoenzyme exhibited a relatively stable state in terms of its potential, absorbance, and ROS scavenging capability. Additionally, this stability can be linked to the interactions between chitosan nanoparticles and two types of nanoenzymes. The positively charged CS NPs, synthesized through ion crosslinking, can adsorb negatively charged GOx and Zn-POM via electrostatic interactions, thereby forming a cascade catalytic system on their surface that creates a unique spatial effect. The reaction rate is positively correlated with the concentration of Zn-POM and negatively correlated with the pH value.[165]

Platelets are intimately associated with the proliferation of endothelial cells and exhibit a range of particular membrane proteins, such as GPIIb, GPIbα, and P-selectin (CD62p), mostly present on active platelets. These proteins facilitate platelet adhesion to injured vasculature, promote the release of growth factors, and expedite angiogenesis.[166,167] Dong and his team created a hydrogel dressing (PLTm@CNPs/Gel) using PLTm-encapsulated cerium oxide nanoparticles loaded in GelMA hydrogel to promote angiogenesis and improve the wound microenvironment. Specifically, the PLTm component was found to enhance impaired angiogenesis in diabetic wound healing, while CNPs effectively altered the harmful oxidative stress-damaged microenvironment and improved chronic inflammation at the wound site. The significant synergistic effects between these components enable the PLTm@CNPs/gel dressing to remodel the adverse oxidative wound microenvironment and promote functional vascular growth, leading to faster and higher quality wound healing, including organized collagen fiber alignment and new blood vessel growth.[168]

Conclusion and Discussion

Due to the large population of diabetes patients and the high prevalence of diabetic foot ulcers, many of which have poor prognoses, it is crucial to explore treatment options for chronic wounds beyond traditional therapies. First, we provide an overview of recent research in relevant fields. This review comprehensively examines the role of various types of nanoenzymes in the healing of diabetic foot wounds. It addresses potential pathogenic mechanisms and promotes wound

healing through five dimensions: infection control, glycemic regulation, antioxidative effects, oxygen generation, and enhancement of cellular functions.

Although some traditional techniques, like hyperbaric oxygen therapy and antimicrobial dressings, have demonstrated favorable outcomes in prior clinical investigations, their effectiveness is frequently constrained by inadequate delivery to the local microenvironment. Nanoenzymes have demonstrated the ability to effectively overcome these limitations. Compared to traditional therapies, nanoenzymes exhibit higher targeting capabilities and biocompatibility, enabling them to act within the local microenvironment while minimizing systemic side effects. This highlights their significant potential in enhancing wound healing outcomes.

Second, although nanoenzymes have demonstrated superior physicochemical properties and biological performance in the healing of chronic diabetic wounds, there remains substantial room for improvement regarding their clinical application and widespread commercialization. In the future, further reducing the cost of nanoenzyme use and implementing stricter safety checks are essential issues to address before entering preclinical stages. Future research could focus on reducing the use of precious metals, developing recyclable nanoenzymes, and lowering the toxicity of biomaterials.Additionally, human skin is influenced by various factors, including temperature, humidity, and physical activity, all of which can affect the efficacy of nanoenzymes. Future studies should concentrate on more comprehensive modeling options and incorporate these variables into experimental designs to fully realize the potential of different types of nanoenzymes in treating diabetic foot ulcers.

Furthermore, combining nanoenzymes with advanced biomaterials—such as smart hydrogels and nanofibers—could further optimize their stability and release rates in vivo, ensuring their effectiveness during treatment. Exploring the synergistic effects of these combinations on wound healing will be an important area for future research.

Third, based on previous experiences, the integration of nanoenzymes with other therapeutic approaches may present new research opportunities. We foresee that forthcoming trends will integrate nanoenzymes with diverse targeted delivery systems, facilitating their precise localization to pathological regions while reducing effects on healthy tissue. This will improve both the safety and effectiveness of medicines. Moreover, these systems may enable the on-demand administration of supplementary therapeutic chemicals and cells, hence facilitating personalized therapy regimens customized to the specific clinical conditions of each patient.

In conclusion, nanoenzymes exhibit considerable potential in biomaterial creation and wound healing. Nonetheless, obstacles in clinical implementation and commercialization require additional research and innovation to fully exploit the promise of nanoenzymes as a unique strategy for treating diabetic wounds.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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