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REVIEW

How Transformative Are ROS Responsive Hydrogel Nanoformulations to Treat Refractory Infected Wounds

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Abstract: Controlling infection in bacterial-infected wounds presents a formidable challenge, especially when compounded by additional high-risk factors that hinder the healing process during clinical interventions. Currently, the efficacy of standard therapeutic approaches often falls short, largely attributed to persistent local infections and inflammatory responses that impede healing cascades. In recent years, increasing reports on the management of hard-to-heal infected wounds have highlighted the potential of reactive oxygen species (ROS)-responsive hydrogels to facilitate wound recovery. The capacity of these hydrogels could be greatly enhanced by integrating them with traditional treatments, thereby addressing the complexities of healing in refractory infected wounds. Therefore, based on a thorough review of latest literatures, this paper comprehensively outlines the molecular mechanisms associated with hard-to-heal infected wounds, the role of ROS-responsive hydrogels in promoting healing, and a combined therapeutic strategy for wound control. It is designed to offer valuable insights to inform and advance future investigative efforts in this research field.

Keywords: hard-to-heal infected wounds, reactive oxygen species, ROS, hydrogel, nanoformulations, combination therapy strategy

Introduction

Bacterial infection, a common complication of skin wounds, ranks among the most substantial factors in hindering wound healing.[1,2] Once a wound is formed, it sequentially undergoes four critical stages – hemostasis, inflammation, proliferation and remodeling – to ensure a successful healing process.[3–5] If bacterial infection occurs in a wound and suffers an ineffective treatment, however, the wound would stay in the inflammatory stage for an extended time.[6,7] At present, the therapy of infected wound mainly relies on the use of local or systemic antibiotics.[8] Recently, some new treatment modalities have developed, including photothermal/photodynamic therapy, gas therapy and metal ion therapy, which really promote the healing of infected wounds to a certain extent;[9–12] but several clinical treatment periods have witnessed that infected wounds with high-risk factors like immunocompromised conditions, multi-drug-resistant bacterial infections, large wound areas and poor local nutritional supply, are often difficult to control by using current treatment methods, thereby leading to their chronic refractoriness.[13,14] Worse still, prolonged inflammation in these wounds exacerbates the excessive production of local reactive oxygen species (ROS) that surpass the antioxidant capacity of cells, in turn damaging cellular membranes, proteins and DNA, further hindering vascularization and tissue regeneration.[15–18] Consequently, the wound festers and evolves into a stubborn, infected wound that resists healing. Therefore, efforts from numerous researchers are persistent to develop effective strategies for above wounds, encompassing new antibiotics, more effective antibacterial material, among which ROS-responsive hydrogel dressings are specially outstanding owing to their unique physicochemical property and ability to scavenge ROS effectively.[19,20]

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ROS-responsive hydrogel, as an innovative macromolecular material with a three-dimensional (3D) network structure, exhibits remarkable properties containing superior water absorption, swelling capabilities, permeability, histocompatibility, biodegradability, adjustability, as well as a composition that closely mimics the extracellular matrix.[21,22] Moreover, it has a lack of cytotoxicity and an excellent adhesion to wounds.[21] Leveraging their special ability to interact with ROS, ROS-responsive hydrogels enable the elimination of excessive ROS from refractory wounds. More importantly, based on the 3D structure, they experience ROS-responsive "autolysis" and sequentially release encapsulated drugs, thereby integrating anti-inflammatory, antimicrobial and pro-restorative effects to greatly accelerate the complex wounds healing.[23] Owing to above distinctive attributes, ROS-responsive hydrogels are emerging as promising candidates for ideal wound dressings.[24] Taken together, we hence discuss the molecular mechanisms and strategies for refractory infected wounds, as well as advancements of ROS-responsive hydrogels in wounds healing.

What Do We Understand About Refractory Infected Wounds?

Difficult-to-heal infected wounds are defined by their resistance to achieving satisfactory therapeutic outcomes with current clinical approaches.[25,26] These wounds have suffered a history of failed treatments, which perpetuates the presence of inflammatory cells that persistently generate excessive ROS, culminating in oxidative stress.[27–29] Both radical and non-radical forms of ROS, including hydrogen peroxide and singlet oxygen, impede cell migration and proliferation, thereby prolonging the inflammatory phase of wound healing.[30–32] The potential molecular mechanisms involving ROS-mediated apoptosis and necrosis that contribute to the delay in wound healing process are described as following.

ROS Directly Mediates Apoptosis

ROS has the ability to directly influence the activity of apoptotic effectors such as cysteinyl asparaginase (caspases), Bcl-2, and cytochrome c, thereby initiating apoptosis.[33] The catalytic function of caspases is dependent on the reduced state of Cys in their active site. Studies have shown that low levels of H2O2 can activate caspases, leading to the cleavage of a wide range of substrates (eg, PARP), DNA damage, loss of membrane integrity, and ultimately cell death through apoptosis.[34,35] Mild elevated ROS is shown to induce the expression of Bcl-2 through activation of transcription factors such as NF-κB, as an adaptive response to promote cell survival.[36] In contrast, in response to excessive ROS, JNK can phosphorylate and inhibit Bcl-2 function, allowing apoptotic processes to occur. Excessive ROS can also trigger cytochrome c peroxidase activity, which leads to cardiolipin peroxidation. Oxidized cardiolipin loses its binding affinity for cytochrome c, causing the dissociation and release of cytochrome c into the cytoplasm, ultimately inducing apoptosis.[37,38]

ROS Indirectly Mediates Apoptosis

Excessive ROS can indirectly mediate apoptosis by affecting many signaling pathways. A moderate increase in ROS can hinder apoptosis by activating the NF-κB pathway, thereby maintaining redox balance. However, a substantial increase in ROS can lead to the inactivation of NF-κB, resulting in limited expression of anti-apoptotic proteins (eg, Bcl-xL and XIAP).[39–41] Furthermore, it inhibits the expression of antioxidant genes such as MnSOD which ultimately promotes cell death execution.[42,43] The activation of the SAPK pathway, induced by ROS, triggers apoptosis in cells.[44] Apoptosis-regulated signaling kinase 1 (ASK1) is normally inhibited by the reduced forms of thioredoxin (Trx) or glutamine-reducing protein (Grx). However, increased levels of ROS cause oxidation of Trx and Grx, resulting in the release and subsequent activation of ASK1.[45] This activation leads to the phosphorylation and activation of c-Jun n-terminal kinase (JNK) and p38-MAPK, further activating P53, pro-apoptotic proteins, ultimately inducing cell death.[46,47] JNK also plays a role in inhibiting Bcl-2 function through phosphorylation and promoting the release of cytochrome c from mitochondria, collectively initiating the apoptotic process.[48,49]

ROS-Mediated Cell Necrosis

Normal levels of ROS can regulate the activity of various macromolecules in cells through oxidative modification, thus controlling normal cellular metabolic processes.[50,51] However, chronic infected wounds often exhibit an excessive amount of ROS in local cells, which continuously attack lipids, proteins and DNA, leading to severe and irreversible oxidative damage.[52,53] This directly results in the inactivation of intracellular macromolecules, cell necrosis, and significantly impedes wound healing.[54]

In summary, the chronic non-healing wounds are marked by persistently elevated ROS that scramble cellular metabolism and inflict widespread damage on DNA, proteins and lipids, ultimately driving cells into apoptosis or necrosis.[55] This oxidative assault cripples wound neovascularization, blocks fibroblast proliferation and paralyzes immune-cell phagocytosis, allowing wound infection to gain the upper hand and healing to stall indefinitely. The mechanism by which ROS cause delayed wound healing is shown in Figure 1.

Role of ROS-Responsive Hydrogels in Infected Wound Healing

Up to now, infected wounds have frequently relied on the application of topical or systemic antibiotics, supplemented with photothermal/photodynamic therapy,[59] gas therapy[10] and metal ion therapy.[60] Although antibiotics effectively run in enhancing the healing rate of infected wounds, the prolonged use of antibiotics may elicit genetic mutations in some bacteria that would facilitate the production of drug-resistant genes.[61,62] This has rendered the healing of certain infected wounds challenging, resulting in the development of chronic non-healing wounds. Even with the presence of wound dressings that possess antibacterial capabilities and ensure proper breathability, the complete healing of infected wounds that harbor drug-resistant bacteria continues to be a formidable challenge across various treatment modalities. These chronic, refractory wounds often exhibit high-level ROS locally, which substantially impede wound healing process.[25,63] Considering this, researchers have put forward an innovative dressing – ROS-responsive hydrogel – that is designed to effectively control infection by scavenging excessive ROS and simultaneously releasing various active substances, thus facilitating the healing of these particularly refractory wounds.[64]

Characterization of ROS-Responsive Hydrogels

ROS-responsive hydrogel is a novel type of hydrogel dressing designed to eliminate excessive ROS from wounds.[65] This unique hydrogel is characterized by its intricate, three-dimensional, reticulated macromolecular structure, which affords it

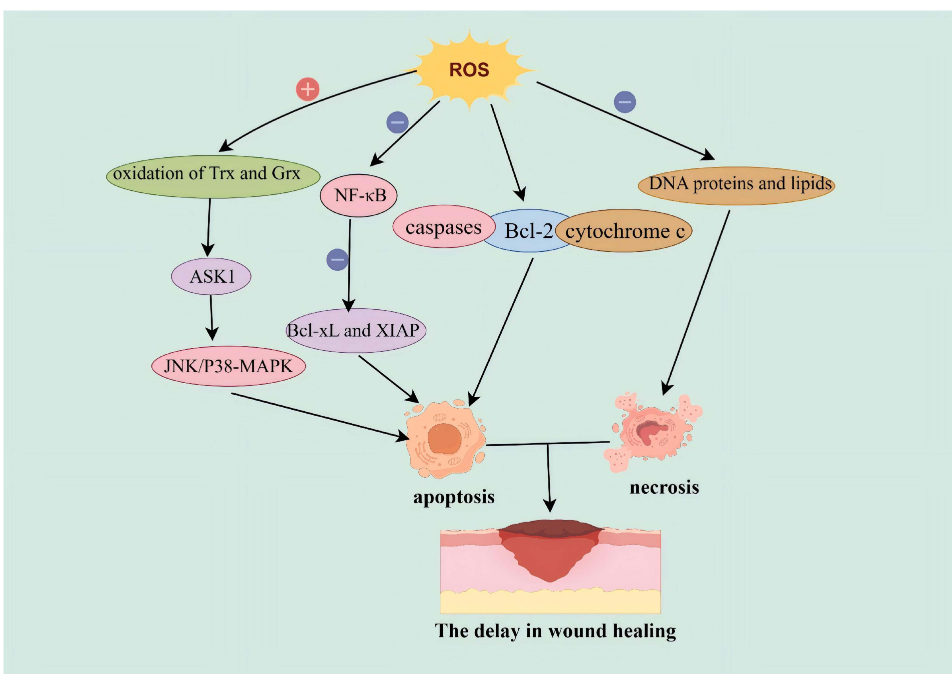

Figure 1 ROS-Driven Mechanisms That Delay Wound Healing. Excessive ROS in the local wound trigger apoptosis through three pathways: oxidizing thioredoxin (Trx) and glutaredoxin(Grx), silencing NF-κB signaling pathway, and directly disabling apoptotic effectors like caspases, Bcl-2, and cytochrome c.[56,57] Additionally, superfluous ROS impair various intracellular macromolecules, eg. DNA, proteins and lipids, through oxidative modification, forcing cells into necrosis. The resulting patchwork of apoptosis and necrosis hinders neovascularization and matrix deposition, leaving the wound trapped in a chronic, non-healing state.[58]

Notes: ⊕ Activate; ⊖ Inactivate.

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carrying a diverse array of active ingredients.[66–68] Its inherent ability to adapt its own structure and physical properties facilitates a precise, controlled release of drugs or targeted effects, remarkably enhancing the wound healing process.[69,70] Boasting exceptional water absorption and swelling capabilities, along with breathability, histocompatibility, biodegradability, adjustability, extracellular matrix-like morphology, non-cytotoxicity, and strong wound adhesion, this hydrogel stands out as a cutting-edge solution in wound healing.[68,71,72] The instinct of ROS-responsive hydrogels interaction with ROS enables them to eliminate excessive ROS from difficult-to-heal infected wounds;[73,74] they, moreover, accurately and sustainably release the encapsulated drugs due to their dynamic structural changes, allowing for a potent combination of anti-inflammatory, antibacterial and pro-restorative effects that in turn expedite the healing process of refractory infected wounds.[75] Consequently, ROS-responsive hydrogels emerge as a compelling choice for optimal wound dressings in the realm of wound care.[76,77]

Mechanism of ROS-Responsive Hydrogels in Scavenging ROS

The defining characteristic that differentiates ROS-responsive hydrogels from conventional hydrogels lies in their ROS responsiveness, which allows them to scavenge excessive ROS at infectious wound sites.[78] The incorporation of ROS-sensitive chemical bonds as responsive moieties constitutes the core strategy for the synthesis of ROS-responsive hydrogels.[79,80] These ROS-sensitive bonds can function either as crosslinkers within the hydrogel network or as integral components of the hydrogel polymer backbone/side chains.[81] In the following section, we will provide a brief overview of the ROS-sensitive bonds/groups that have been reported in the current literature.

Phenylboronic Acid

In the preparation of hydrogels, phenylboronic acid is incorporated as a crosslinker to form boronic ester bonds with the hydrogel polymer backbone.[82,83] When the hydrogel is exposed to a high ROS environment, ROS can coordinate with the boron atom, leading to the formation of phenol and the cleavage of boronic ester bonds.[84] This cleavage disrupts the hydrogel network structure, subsequently triggering the release of other active therapeutic agents encapsulated within the hydrogel, thereby promoting wound healing. Concurrently, phenylboronic acid can also conjugate with drugs, and upon response to reactive oxygen species, the active drugs are released.[85] Li et al integrated phenylboronic acid-modified hyaluronic acid (HP), metal-phenolic networks (CaTA), methacryloylated carboxymethyl chitosan (MA-CMCS), and platelet-rich plasma (PRP) into a hydrogel system. Mediated by the CaTA component linked via dynamic borate ester bonds, this system enables ROS-responsive regulation of inflammatory responses.[69]

Thioacetal/Thioketal

The thione bond is a ROS-responsive covalent bond that can react with several canonical reactive oxygen species (ROS), such as superoxide anion (•O_2^-), hydroxyl radical (•OH), and hydrogen peroxide (H_2O_2), even at a threshold concentration as low as 100 μM, leading to its degradation into acetone and thiol.[86,87] Incorporation of thione bonds into hydrogels confers ROS responsiveness to the hydrogel system.[88] Specifically, upon exposure to ROS at a certain concentration, the hydrogel undergoes cleavage or other reactions, which scavenges excess ROS and triggers the intelligent release of other encapsulated therapeutic agents from the hydrogel matrix.[23,89]

Metal Nanoparticles

The incorporation of specific metal ions into hydrogels enables the scavenging of excess ROS at the wound site via redox cycling between the oxidized and reduced states of the metal ions. Metal ions are frequently incorporated into ROS-responsive hydrogels in the form of nanoparticles, including cerium oxide nanoparticles, ferrocene, manganese dioxide nanoparticles, and the like. For example, Cheng et al embedded cerium oxide nanoparticles within hydrogel dressings. Leveraging the redox transition between Ce^{3+} (reduced state) and Ce^{4+} (oxidized state), the system effectively diminishes ROS levels, thereby conferring ROS responsiveness to the hydrogel.[90] Tian et al engineered a smart hydrogel using carboxymethyl chitosan (CMCS) as the primary polymeric scaffold Dynamic, reversible cross-links were established via host–guest interactions between β-cyclodextrin (βCD) and ferrocene (Fc).[91] Leveraging ferrocene's redox-active nature—capable of switching between oxidized and reduced forms—the hydrogel effectively scavenges surplus ROS, thereby accelerating wound repair.[91–93] Song et al successfully incorporated manganese dioxide microparticles into a multifunctional hydrogel.[94]

Manganese dioxide not only exerts bactericidal effects via photothermal therapy (PTT) but also catalyzes the decomposition of hydrogen peroxide and releases oxygen, thereby effectively ameliorating the inflammatory microenvironment.[94] Consequently, the hydrogel significantly promotes cell proliferation, migration, angiogenesis, collagen deposition, and tissue regeneration.[94]

Mechanisms of ROS-Responsive Hydrogels Promoting Wound Healing

Numerous studies have demonstrated that ROS-responsive hydrogel dressings significantly enhance the healing process of various difficult-to-heal infected wounds. The ROS-responsive hydrogel encouraging wound recovery involves a variety of specific mechanisms, mainly containing excessive ROS elimination, redox balance restoration, antimicrobial activity, and the provision of a environment conducive to wound healing.[25,95,96] The mechanism by which ROS-responsive hydrogels accelerate infected wound healing is shown in Figure 2.

Scavenging Excessive ROS and Regulating Redox Balance

The unique structure of ROS-responsive hydrogel specifically favors the removal of excessive ROS from the wound site, whether in vivo or vitro. By restoring ROS levels to the normal state, this intervention halts the assault on lipids and other macromolecules, thereby averting the formation of free radicals and the ensuing chain reactions.[99] The mild elevation of ROS initially triggers the NF-κB pathway, which then enhances the expression of anti-apoptotic proteins like Bcl-xL and XIAP, effectively arresting the execution of cell death.[100,101] Concurrently, the SAPK pathway remains inactive, while the MAPKK-JNK one does active, resulting in diminished production of P53 and pro-apoptotic proteins.[102] This cascade of events leads to a reduction in local necrosis and apoptosis within the wound area, thereby facilitating wound healing.

Upregulation of M2-Phenotype Macrophages Polarization

Macrophages chiefly differentiate into pro-inflammatory (M1) and anti-inflammatory (M2) types in the process of wound healing.[103] M1 macrophages are essential for clearing microorganisms and mediating inflammation at injury sites, while M2 macrophages play a crucial role in promoting anti-inflammatory effects, modulating wound adhesion, diminishing

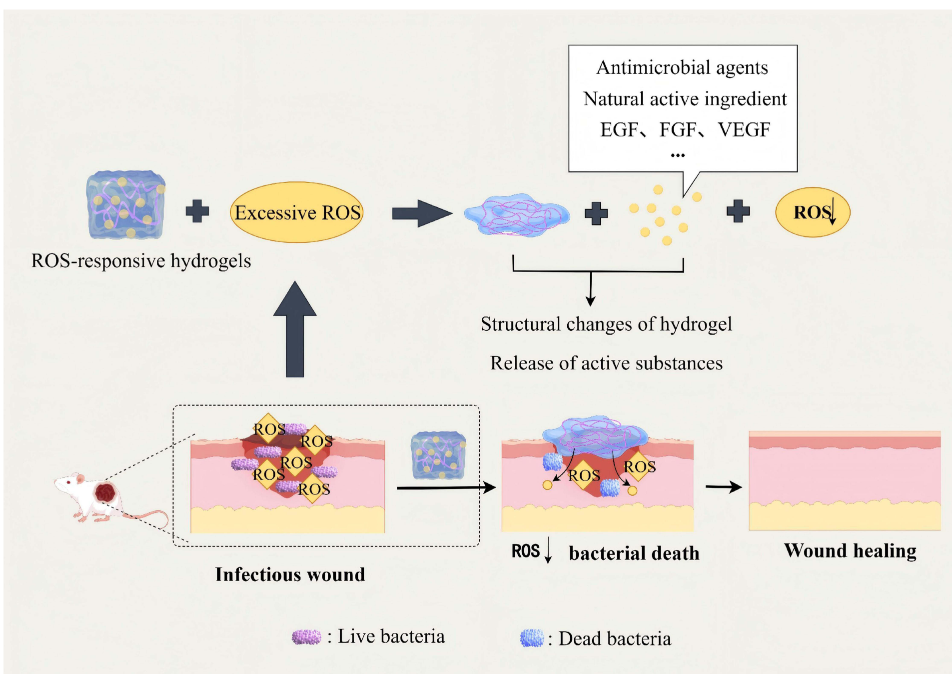

Figure 2 Mechanisms of ROS-Responsive Hydrogels Accelerating Infected-Wound Healing. Upon exposure to the ROS-rich milieu of infected wounds, ROS-responsive hydrogels interact with ROS, scavenge excess radicals and undergo in-situ structural rearrangement.[54] This "on-demand" reaction steadily releases antibacterial agents, bioactive natural compounds and growth factors, simultaneously deactivating bacteria and quelling oxidative stress—creating a microenvironment that resists inflammation response and accelerates tissue repair.[97,98]
Note: ↓ indicates downregulation.

inflammation, and facilitating angiogenesis and tissue regeneration. In the late inflammatory phase of normal wounds, a gradual transition from M1 to M2 macrophages emerge along with healing progresses.[104] However, some detrimental factors like bacterial infections could disrupt this polarization, resulting in persistent inflammation within the wound environment. Such interference would impair epithelial regeneration, collagen deposition and angiogenesis.[104–106] The use of ROS-responsive hydrogels effectively scavenges local ROS and above harmful factors, which in turn encourages M2 macrophages polarization and amplifies anti-inflammatory responses, eventually accelerating the wound healing process.[107,108]

Establishment of a Microenvironment Conducive to Wound Healing

Besides eliminating ROS, ROS-responsive hydrogels also possess all the characteristics common to general hydrogels, featuring hydrophilicity and water retention, being non-cytotoxic, and adhering well to wounds and being easily detached from the wound surface.[109] When applied to infectious wounds, ROS-responsive hydrogels can absorb the excessive local exudate, maintain a moist environment, and protect the wounds from further infection.[20] In a word, ROS-responsive hydrogels, while protecting wounds, also offer a favorable local environment for wound healing.

Loading Active Pharmaceuticals

ROS-responsive hydrogels are provided with superior adjustability.[66,70] Consequently, researchers have incorporated active substances such as antibiotics, natural antibacterial substances, nanoparticles, and growth factors into ROS-responsive hydrogels via various means, including encapsulation, during the preparation process, thereby enabling the sustained local release of various active drugs for wound healing. This targeted carrier approach focuses drugs at the infected wound site, preventing drug inactivation and minimizing the potential adverse effects typically associated with systemic medication to the greatest extent. We will further describe this combined treatment in the next section.

How Advanced are ROS Responsive Hydrogels to Treat Infected Wounds?

Although ROS-responsive hydrogels exhibit excellent biocompatibility and notable anti-inflammatory/antibacterial properties, their standalone capacity to combat bacteria and promote wound healing tends to be insufficient, thus leading to uniform therapeutic outcomes. To increase the effectiveness of these hydrogels in infected wound healing, researchers spare no effort in their integration with traditional treatment modalities. Therefore, some latest developments in combination therapies, ie, ROS-responsive hydrogels dressings combined with other vehicles such as antibiotics, photothermal/photodynamic therapy, gas therapy, metal ion therapy and pro-angiogenic therapy, are described as follows in order to guide their practical application in clinic. ROS-responsive hydrogel combination therapy is shown in Figure 3.

ROS-Responsive Hydrogels in Combination with Antibiotics

Antibiotics, whether systemic or topical application, are the mainstay for treating infections; however, the increase of drug-resistant bacteria has diminished the drug's efficacy.[112] Incorporating antibacterial agents into ROS-responsive hydrogels offers a targeted and controlled release strategy, effectively scavenging excess ROS and maintaining redox balance within infected regions. This innovative approach has been exemplified by the work of Qiao et al who prepared ROS-responsive HA-PBA/PVA (HPA) hydrogel through the crosslinking of hyaluronic acid grafted 3-aminophenylboronic acid (HA-PBA) and polyvinyl alcohol (PVA) via phenylboronic acid ester bonds.[113] Then, they loaded hydrophilic moxifloxacin (M) and hydrophobic curcumin (Cur) into the HPA hydrogel to achieve the combined treatment of antibiotics and ROS-responsive hydrogel, obtaining HPA/M&Cur-PF.[113] Through in vitro drug release experiments, they found that HPA/M&Cur-PF could rapidly release moxifloxacin and curcumin in the presence of H2O2, eliminating ROS while controlling bacterial infection. By establishing a mouse skin wound model infected with MRSA, they found that on the 7th and 14th days after administration, the wound closure rate in the HPA/M&Cur-PF group was significantly higher than that in the HPA group, suggesting that the combination of ROS-responsive hydrogel with antibiotics or other antibacterial substances has a significantly better therapeutic effect on refractory infectious wounds than using ROS-responsive hydrogel alone.[113] Hu et al engineered a novel ROS-responsive nano-hydrogel by grafting phenylboronic acid onto alginate polymer chains, creating a system that provides localized antimicrobial and anti-inflammatory effects via

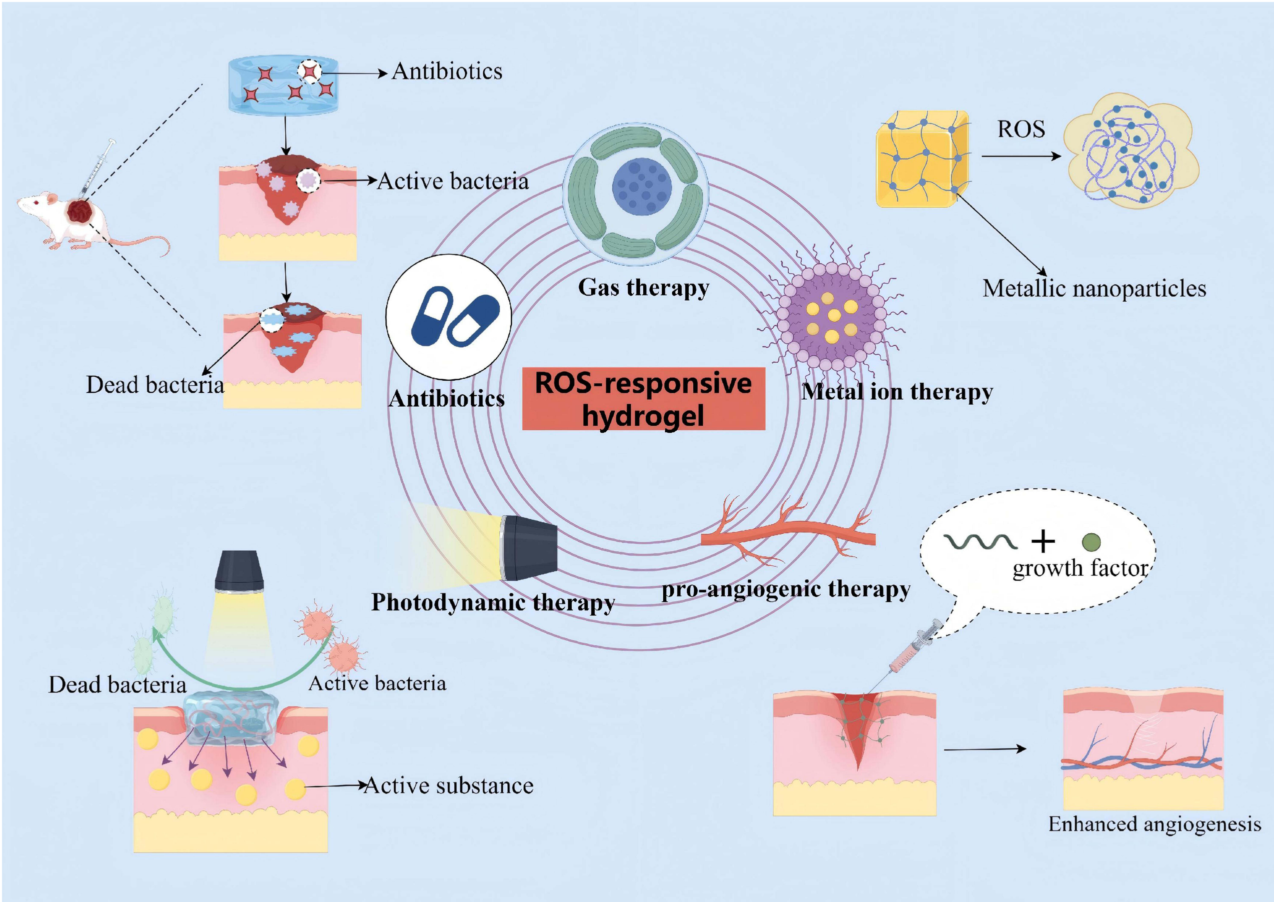

Figure 3 ROS-Responsive Hydrogel Combination Therapy Strategies for Refractory Infected Wounds. ROS-responsive hydrogels are now integrated into five dominant combination paradigms: ROS-responsive hydrogels with antibiotics, ROS-responsive hydrogels with photothermal/ photodynamic therapy, ROS-responsive hydrogels with gas therapy, ROS-responsive hydrogels with metal ion therapy, and ROS-responsive hydrogels with angiogenesis therapy—each exploiting the ROS-triggered "on-demand" switch to synchronize antimicrobial potency with tissue repair.[110,111]

preloaded with amikacin (AM) and naproxen (Nap).[114] Their hydrogel has been demonstrated remarkable efficacy, reaching an inhibition rate of 90% against *Staphylococcus aureus* and 98% against Pseudomonas aeruginosa.[114] Meanwhile, Zhao et al presented a hydrogel synthesized by cross-linking polyvinyl alcohol (PVA) with ROS-responsive linkers, designed to scavenge ROS.[25] This hydrogel is impregnated with mupirocin and granulocyte-macrophage colony-stimulating factor (GM-CSF), and it gradually disintegrates under conditions of high reactive oxygen species (ROS), thereby releasing mupirocin and GM-CSF, that are vital contributors to infected wounds healing.[25] It can effectively kill *Staphylococcus aureus* in the simulated microenvironment of a wound in vitro.[25] The in vivo experiments revealed that after the hydrogel loaded with mupirocin was applied to the *Staphylococcus aureus*-infected wounds on the backs of mice for 16 hours, the colonization of *Staphylococcus aureus* at the wound site was significantly decreased.[25] Cao et al deposited [2-(acryloyloxy)ethyl]trimethylammonium chloride (Bio-IL) and gelatin methacryloyl (GelMA) onto a doxycycline hydrochloride (DOXH)-loaded, reactive oxygen species (ROS)-degradable polyurethane (PFKU) nanofiber membrane via three-dimensional (3D) printing technology. Subsequent ultraviolet (UV) irradiation yielded conductive hydrogel strips. Notably, in a high ROS environment, the release rate of DOXH was significantly enhanced.[115]

ROS-Responsive Hydrogels in Combination with Photothermal/Photodynamic Therapy

Conventional photothermal therapy (PTT) and photodynamic therapy (PDT) often generate excessive ROS, which, while effective in inhibiting bacterial growth, may also trigger inflammation that further delays tissue regeneration and wound healing. However, integrating photosensitizing materials into ROS-responsive hydrogels achieves a synergistic therapeutic strategy,

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namely merging these hydrogels with photosensitizers employed in PTT or PDT. The incorporation of these materials confers a multitude of advantages, such as hemostasis in wounds, modulation of immune microenvironment, promotion of M2 macrophage polarization, antibacterial activity, enhancement of local angiogenesis and improvement of epithelial regeneration. Critically, this strategy favors the maintenance of redox balance, as it prevents the excessive ROS-induced damage to tissue cells, holding promise for applications in wound recovery. The typical combined approach was implemented by Wang et al, who developed an innovative, injectable bio-excited MnO2 hybrid hydrogel that responded to both redox and light stimuli (BMH).[116] This cutting-edge hydrogel has demonstrated remarkable efficacy in accelerating wound healing, particularly in cases of multidrug-resistant infections, mainly through efficiently eradicating bacterial invasion and concurrently mitigating OS and inflammation within the wound's microenvironment.[116] Furthermore, reports from Wang et al showed an Ag/TiO2-doped PVA-hybridized hydrogel with potent bacteriostatic activity against Escherichia coli and *Staphylococcus aureus*, attributed to ROS release from its photodynamic effect under 660 nm visible light.[116] In addition, Luo et al have crafted a novel near-infrared (NIR) photothermal hydrogel by incorporating α-lipoic acid-modified palladium nanoparticles into calcium ion-crosslinked sodium alginate matrix.[117] This injectable hydrogel adeptly convers NIR light into localized hyperthermia, achieving the elimination of over 80% of E. coli or S. aureus and more than 60% of ROS in cells;[117] it meanwhile downregulates the gene levels of TNF-α and IL-18 by 52.9% and 53.3%, respectively.[117] Herein, Zhu et al designed PDA@MnO@CuO (PMC) nanoparticles using the high-efficiency photothermal agent polydopamine (PDA) as the core, along with manganese dioxide (MnO_2) and copper oxide (CuO).[118] The PMC nanoparticles and taurine were encapsulated in a polysaccharide-based hydrogel (FH) consisting of Falcaria vulgaris gum (FG) and hyaluronic acid (HA), thereby forming the FH-PMC-T hydrogel.[118] The capacity of the FH-PMC-T hydrogel combined with mild photothermal therapy (PTT) to promote wound closure and functional skin regeneration was validated using a full-thickness rat wound model.[118]

ROS-Responsive Hydrogels in Combination with Gas Therapy

Although traditional gas therapy has positive effects on wound healing, it faces numerous limitations including the risk of sudden release, a short half-life, high reactivity and the possibility of producing carcinogenic by-products. However, through incorporating materials that generate therapeutic gases (eg, nitric oxide, hydrogen, oxygen, carbon monoxide and hydrogen sulfide) into ROS-responsive hydrogels, this innovative approach surpasses the conventional, intermittent ROS-triggered one owing to its prolonging the gas therapeutic effect and accelerating wound healing, thus offering a more sustained and effective prospect. Similarly, Yu et al have devised a cutting-edge sustainable wound healing system that leverages a H2O2-degradable hydrogel paired with a biosafe NO donor, l-Arginine, and employs low concentrations of H2O2 to rapidly address bacterial-infected open wounds.[119] Within this system, l-Arginine is perpetually stimulated by H2O2, leading to the production of NO and in turn facilitating the chemotaxis of macrophage and fibroblast towards the wound site, as well promoting collagen synthesis.[119] Consequently, this breakthrough approach rapidly enhances wound healing and skin regeneration.[119] Moreover, the dynamic duo of H2O2 and NO exhibits a potent synergistic interaction, bolstering antimicrobial capabilities against the notoriously stubborn ampicillin-resistant Escherichia coli.[119] In a groundbreaking study, Chen et al unveiled a hydrogen-producing hydrogel crafted from live Chlorella vulgaris and bacteria, capable of sustaining hydrogen generation for an impressive 60 hours—a feat that outshines the fleeting efficacy of traditional therapies;[120] this hydrogel not only exhibits outstanding antioxidative properties but also efficiently scavenges ROS, paving the way for effective healing in chronically infected wounds.[120] Coincidentally, Li pioneered a novel approach by enveloping the photosynthetic bacterium Spirulina platensis (SP) with carboxymethyl chitosan to create SP gel;[121] this gel continuously produces oxygen, effectively combating acute or chronic tissue hypoxia.[121] When subjected to 650 nm laser irradiation, SP releases chlorophyll, acting as a natural photosensitizer that generates ROS to photodynamically destroy bacteria in infected areas, thereby hastening wound healing.[121] Ye et al developed a ROS-responsive DNA hydrogel (LGAH), into which ginseng-derived exosomes (G-Exos) and the nitric oxide (NO) donor L-arginine (L-Arg) were incorporated.[110] Upon laser irradiation, L-Arg generates NO, and the synergistic effect of these components promotes the healing of infected wounds.[110]

ROS-Responsive Hydrogels in Combination with Metal Ion Therapy

For preferable treatment of refractory infected wounds, researchers have proposed incorporating some bacteriostatic metal ions (eg, Ag+, Zn2+, Cu2+) into ROS-responsive hydrogels, in favor of boosting antimicrobial properties and minimizing tissue irritation and toxicity. As a typical example, Hu et al have developed a novel ROS-responsive antimicrobial hydrogel, PAAg-PGFe, by integrating poly (acrylic acid) (PA), silver nanoparticles (AgNP) and polyglutamic acid (PG) enriched with Fe2+/Fe3+ ions;[122] this hydrogel maintains its stability under normal conditions but swiftly disaggregates in the presence of ROS, triggering substantial oxidative stress that effectively eradicates bacteria–particularly Pseudomonas aeruginosa.[122] Similarly, a versatile hydrogel (HA@Cur@Ag) has been ingeniously engineered by Shi and Chen et al who incorporated curcumin liposomes and AgNPs trading on the crosslinking between mercapto hyaluronic acid (SH-HA) and disulfide-bonded hyperbranched poly (ethylene glycol) (HB-PBHE) via a Michael addition reaction, boasting a suite of impressive properties, including ROS scavenging, bacteriostatic activity, anti-inflammatory effects, and angiogenesis promotion.[123] Yet again, Bochani et al have developed a chitosan-based hydrogel, CT-TA-Fe-MnO2, that incorporates tannic acid (TA), iron (Fe) and manganese dioxide nanosheets; findings from experiments in vitro and in vivo not only confirmed its potent antimicrobial properties and wound-healing capabilities, but also revealed that CT-TA-Fe-MnO2 rarely affected vital organs, instead, reducing hemostasis time, enhancing anti-inflammatory responses and accelerating wound healing within 14 days.[124] Zhang et al developed an infection-responsive antibacterial hydrogel (CBGCT), which is reinforced with copper ion-tannic acid nanosheets (Cu@TA) and guar gum. Upon exposure to acidic pH conditions or elevated reactive oxygen species (ROS) levels, the pH-responsive degradation behavior of Cu@TA nanosheets enables the sequential controlled release of copper ions and tannic acid from the CBGCT hydrogel, thereby potentiating angiogenesis and anti-inflammatory effects.[125]

ROS-Responsive Hydrogels in Combination with Pro-Angiogenic Therapy

In the proliferation stage, wounds are contingent upon cellular proliferation to encourage the formation of new granulation tissue. Apart from factors like infection and oxidative stress, local angiogenesis disorders are also crucial factors hindering the healing of refractory infectious wounds. The topical application of various growth factors contributes to elevation of cell proliferation, promotion of neovascularization and acceleration of wound healing. However, when applied directly, these growth factors quickly become inactive, thereby hindering their therapeutic efficacy.[126] To enhance the proliferation phase of wound healing, numerous researchers spare no effort in developing a ROS-responsive hydrogel that incorporates diverse growth factors to promote angiogenesis. Encapsulating epidermal growth factors, transforming growth factors, fibroblast growth factors and others within ROS-responsive hydrogels affords them long-term maintenance of biological activity and a sustained release into wounds, hence optimizing their wound healing potential. This strategy effectively stimulates cell proliferation and angiogenesis, and enhances the nutritional supply to the wound area through upregulating angiopoietin-1 expression in wound cells and recruiting endothelial progenitor cells. The local continuous release of active growth factors is accomplished by the combination therapy of ROS-responsive hydrogels and growth factors, thereby accelerating wound healing. Zhu et al reported a ROS-responsive hydrogel loaded with fibroblast growth factor and metformin.[127] In their research, it was uncovered that this hydrogel could potently recruit endothelial progenitor cells (EPCs) to promote angiogenesis and wound healing via upregulating ang1 expression.[127] Likewise, Wang et al have designed an integrated hydrogel, called ITG-PEGDA@SA that is composed of polyethylene glycol/alginate, which inside serves as a ROS scavenger whereas the external sodium alginate layer degrades into a platform that delivers recombinant human epidermal growth factor (rhEGF), exhibiting a substantial promise for enhancing wound repairing and healing[128] An et al synthesized a polyethylene glycol (PEG) responsive injectable hydrogel containing a thioketal bond (PEG-TK hydrogel), and combined it with epidermal growth factor (EGF) to obtain EGF@PEG-TK hydrogel.[76] This hydrogel can eliminate excessive reactive oxygen species (ROS) at the local wound site and achieve sustained release of EGF.[76] The in vivo experimental results indicated that the wound closure rates of PEG-TK and EGF@PEG-TK hydrogels for full-thickness skin defect wounds in Sprague-Dawley (SD) rats reached 88% and 90%, respectively, both higher than that of the control group (79%).[76]

The Future Prospective

Recent years have seen a surge in interest towards hydrogels, particularly ROS-responsive hydrogels, for treating infected wounds. These cutting-edge wound dressings go beyond the conventional capabilities of traditional hydrogels through effectively scavenging excess ROS, stimulating angiogenesis, exhibiting antimicrobial effects, and boosting M2 macrophage activity, all of which contribute significantly to enhanced wound recovery. Researchers are now looking into blending ROS-responsive hydrogels with traditional therapies to unlock synergistic benefits and enhance their therapeutic impact. However, the field of these hydrogels is still in its infancy. Major challenges include striking a wider balance of ROS, maintaining the hydrogel's stability at the wound site, and refining the dressing's precision and responsiveness. In summary, ROS-responsive hydrogel dressings still face several critical challenges and hurdles prior to clinical translation. Firstly, long-term safety assessments remain insufficient.[129] ROS-responsive hydrogels typically have complex compositions, and the cleavage of ROS-responsive linkages may generate novel small-molecule byproducts—yet the potential adverse effects of these metabolites on host tissues have not been fully elucidated.[130] Secondly, precise spatiotemporal regulation of drug release remains elusive. Given the substantial inter-individual and intra-tissue variability in endogenous ROS levels, active therapeutic agents encapsulated within the hydrogels are at risk of either "burst release" (premature rapid release) or "incomplete release" (insufficient drug delivery over the treatment window).[131] Thirdly, clinical validation data are currently lacking. Most existing studies rely solely on animal models to evaluate safety profiles and therapeutic efficacy, with limited evidence from well-designed clinical trials to support their translational potential.[132]

Owing to the limitations in the authors' expertise and professional scope, this study does not encompass the chemical synthesis methods and specific mechanisms of reactive oxygen species (ROS)-responsive hydrogels. Thorough research is crucial for developing effective ROS-responsive hydrogels suitable for clinical applications. Future research may further focus on the development of hydrogel formulations with enhanced stability, sensitivity, and safety, so as to accelerate the clinical translation of reactive oxygen species (ROS)-responsive hydrogels.[133]

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Author Contributions

Hongqiong Xiang, Zongjunlin Liu and Jianqiao Zhong were responsible for the design of conception and design. Hongqiong Xiang and Lina Cai contributed to the formation of the draft of the manuscript. Ke Xian, Jianqiao Zhong and Zongjunlin Liu are responsible for the design of figures in the manuscript. 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

The authors report no conflicts of interest in this work.

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