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Reactive Oxygen Species in Wound Healing, Balancing Damage and Repair: A Literature Review

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ABSTRACT

Reactive oxygen species (ROS) are molecules produced intracellularly during mitochondrial respiration and through enzymatic activity such as NADPH oxidases, xanthine oxidases, and peroxisomes. During wound healing, ROS functions as both a signalling molecule and damages the tissues and this is termed “ROS paradox”. During the inflammatory phase of wound healing, NADPH oxidase produces ROS, strengthening the respiratory burst in macrophages and neutrophils for the clearance of microbes. To preserve wound sites, during hemostasis phase, ROS assists with vasoconstriction and aggregation of platelets. ROS can act as signalling molecules which enhances the activation of vascular endothelial growth factor (VEGF), leading to production of fibroblasts, angiogenesis and migration of kerationocytes. ROS plays an important part during the remodeling phase by controlling the tensile strength and scarring of tissues by being involved in collagen cross linking and extracellular matrix turnover. However, excess concentration of ROS slows the healing process and increases degradation of the ECM, lipid peroxidation, DNA damage and oxidation of protein leading to chronic wound states. Current treatment methods aim to regulate ROS through advanced delivery systems involving cerium oxide nanoparticles, antioxidant mediated therapies using compounds like circumin and N-acetylcysteine, and regulated pro-oxidant therapies like photodynamic therapy. By understanding and studying the dual nature of ROS, the mutual aim of emerging therapeutic approaches for optimal wound healing is to restore the redox equilibrium and a few examples include, antioxidants targeting mitochondria, redox responsive biomaterials and ROS scavenging hydrogels.

Keywords: reactive oxygen species, wound healing, oxidative stress, redox signaling, antioxidants, chronic wounds.

INTRODUCTION

Reactive oxygen species (ROS) such as superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radicals (•OH) are highly reactive molecules that are synthesized endogenously in the body. Their principal sources are mitochondrial respiration, where electron leakage by complexes I and III of the electron transport chain produces O_2^-, and enzymatic systems such as NADPH oxidases (NOX), xanthine oxidase, and peroxisomes [1]. These molecules are tightly regulated by endogenous antioxidant mechanisms in an attempt to prevent cell damage. As for wound healing, ROS not only represent metabolic waste but have critical physiological roles.

During the hemostasis phase, ROS facilitate platelet aggregation and vasoconstriction to stabilize the wound site. When healing proceeds to the inflammation phase, ROS, especially H_2O_2 produced by NADPH oxidase, enhance the respiratory burst in macrophages and neutrophils to help kill microbes and phagocytose. Low ROS levels are proliferative phase signaling molecules that induce keratinocyte migration, fibroblast proliferation, and angiogenesis through enhanced vascular endothelial growth factor (VEGF) and other growth factors. ROS participate in collagen cross-linking and extracellular matrix (ECM) turnover in the remodeling phase and control tissue tensile strength as well as scarring [2].

However, this physiologic involvement becomes pathological when ROS concentration exceeds antioxidant buffering capacity. Exuberant ROS increase lipid peroxidation, protein oxidation, DNA damage, and ECM degradation, halting healing and propagating chronic wound states. Such is the "ROS paradox": while physiologic levels of ROS are critical to effective tissue repair, their exuberant levels induce oxidative stress, slowing or even halting wound resolution [3].

Understanding and targeting this dual nature has given rise to new therapeutic strategies, including mitochondrial targeted antioxidants, redox-responsive biomaterials, and ROS-scavenging hydrogels, with the shared objective of restoring redox balance [3]. This review will consolidate the current understanding of ROS roles in wound healing and evaluate promising therapeutic avenues taking advantage of or opposing their activities.

Dual Role of Reactive Oxygen Species (ROS) in Wound Healing

Beneficial Roles of ROS (Low/Moderate Levels)

The role of reactive oxygen species plays a variety of roles in wound healing. While low to moderate levels are essential for antimicrobial defense and signaling pathways which regulate cell proliferation and tissue repair, excessive and prolonged ROS production can lead to oxidative stress, tissue damage, and impaired wound healing [4, 5, 6]. Through NADPH oxidase, injury first causes phagocytes (macrophages, neutrophils) to undergo an oxidative burst. With the help of myeloperoxidase and superoxide dismutase these cells transform O_2^- into superoxide (O_2^-) and subsequently H_2O_2, HOCL, and •OH radicals [1, 3]. This local ROS surge sterilizes the wound bed and modulates repair [4, 5, 7].

Controlled production of ROS (e.g., H_2O_2 by platelets and phagocytes) controls hemostasis and antimicrobial protection during the initial stage of wound healing. Platelet-derived ROS evoke vasoconstriction and clotting, while H_2O_2/HOCl induce killing of invading microbes [1, 3]. Also, local ROS trigger the release of pro-inflammatory cytokines and chemo attract neutrophils and monocytes (e.g., TNF, PDGF) that facilitate enhanced killing of the pathogen, creating a sterile environment which is essential for the healing cascade [5, 7]. ROS also triggers the release of key growth factors like VEGF, PDGF, and TGF-β that cause angiogenesis, cell proliferation, and granulation tissue formation. These activities provide support for keratinocyte migration and proliferation and fibroblast activation, which are important in re-epithelialization and ECM formation [4].

In low to moderate concentrations, ROS are signaling molecules that govern the process of wound healing. HIF-1α stabilization and ROS-stimulated kinase activation (MAPK, PI3K/Akt) guarantee endothelial cell migration, growth, and tube formation, all vital to angiogenesis [4, 6]. Similarly, ROS trigger transcriptional cascades (by NF-κB, AP-1) in fibroblasts and keratinocytes and activate cell growth, migration and ECM production [5]. Low-level ROS also enhance the upregulation of collagen prolyl hydroxylase, which facilitates maturation of collagen [8]. In general, well-balanced ROS control leukocyte recruitment, angiogenesis, keratinocyte re-epithelialization and extracellular matrix remodeling in normal healing.

Harmful Roles of ROS (High/Prolonged Levels)

Oxidative stress occurs when ROS production exceeds antioxidant capacity. High concentrations of ROS overwhelm enzymes like superoxide dismutase (SOD), catalase, and glutathione peroxidase, leading to indiscriminate damage to cellular components [4, 5]. ROS peroxidize lipids within cell membranes (form MDA, 4-HNE), oxidize protein thiols/carbonyls, and cause DNA strand breaks (8-OHdG formation) [4]. Biochemical damage impairs cell viability: keratinocytes and fibroblasts have reduced proliferation/migration under oxidative conditions. ROS-stimulated NF-κB/TNF-α signaling also promotes upregulation of matrix metalloproteinases (MMPs) (MMP-1, -2, -3, -9), which degrade collagen and ECM constituents [4]. The collective consequence of excessive ROS is compromised epithelialization and granulation, and a shift to tissue degradation.

Increased ROS continuously is the cause of wound pathophysiology in chronic wounds. Oxidative stress also triggers senescence: damage to DNA and induction of p53 by ROS result in a senescence-associated secretory phenotype (SASP). Senescent immune cells and fibroblasts discharge pro-inflammatory cytokines, ROS, and MMPs, maintaining ECM degradation and inflammation [4]. At the same time, ROS suppress angiogenesis – e.g., by disrupting HIF-1α/VEGF signaling – with resulting impaired neovascularization [4]. The chronic wound environment is thus marked by profuse biofilms, elevated protease activity, ECM degradation, and hypoxia [4, 5]. In this setting, growth factor signaling is muted and cell motility is arrested, so the wound gets stalled in inflammation.

In Vitro vs. In Vivo Insights

In vitro systems have been instrumental in defining the specific signaling pathways through which ROS has an action on wound healing. In culture, treatment with precise levels of ROS has been described to activate fibroblast proliferation, keratinocyte migration, and expression of angiogenic factors. Mechanistically, this occurs through ROS-mediated activation of pathways such as NF-κB and Nrf2. NF-κB promotes pro-inflammatory gene expression and keratinocyte migration, while Nrf2 regulates antioxidant response, creating a redox balance environment that promotes healing [5]. Additionally, in vitro dose-response studies have offered proof for the establishment of threshold levels of ROS promoting cell proliferation compared with levels of ROS inducing oxidative damage or apoptosis [5].

However, in vivo models reveal a more complex situation. Diabetic and ischemic wound animal models, for example, reveal that ROS kinetics are regulated by numerous extrinsic and systemic factors such as immune reactions, microcolonization, and tissue oxygenation. For example, diabetic mice studies revealed that Nrf2 activators promote the healing of wounds by reducing oxidative stress and enhancing growth factor expression [9]. But this translation to human clinical practice has not been consistent, likely due to interspecies differences, metabolic heterogeneity in the system, and environmental heterogeneity. The presence of immune system and microbiome also regulate ROS effects in vivo, echoing the

limitations of simplistic in vitro findings and demanding integrative models [9].

Clinical Relevance & Implications

Clinically, ROS levels are significantly elevated in chronic wounds, especially in conditions such as diabetic ulcers, venous leg ulcers, and pressure injuries [5]. These wounds are often characterized by prolonged inflammation, high bacterial burden, and impaired angiogenesis, all of which are exacerbated by oxidative stress. Elevated biomarkers such as malondialdehyde, 4-hydroxynonenal, and protein carbonyls are frequently detected in chronic wound exudates and tissue samples [5, 10]. These markers provide valuable insight into the redox state of the wound and may serve as prognostic tools.

Several clinical interventions have been developed to counteract oxidative stress in wounds. Hyperbaric oxygen therapy (HBOT), for instance, increases tissue oxygen tension and paradoxically induces moderate ROS to stimulate angiogenesis while ultimately reducing chronic oxidative stress through improved perfusion and cellular metabolism [5]. Topical antioxidants such as alpha-lipoic acid, N-acetyl cysteine, and natural compounds like curcumin have also demonstrated potential in clinical and preclinical studies by decreasing oxidative markers and promoting re-epithelialization [10]. Nevertheless, because ROS levels and responses vary between individuals, a one-size-fits-all approach may not be effective. Personalized treatment protocols that monitor oxidative biomarkers and tailor antioxidant therapy accordingly could offer a more precise and effective wound management strategy.

Therapeutic Interventions on ROS in Wound Healing and Future Perspectives

Antioxidant-Based Therapies

Natural Antioxidants

Inflammatory and oxidative stress-modulating compounds, including curcumin, N-acetyl cysteine (NAC), and resveratrol, influence wound healing development [11, 12].

The mode of action of curcumin has been reported to be due to its free radical scavenging property, stimulation of mitochondrial enzymes like Mn-SOD and catalase, and inhibition of major inflammatory molecules like NF-κB and COX-2 [12]. NAC is known to enhance the antioxidant defense system by directly neutralizing reactive oxygen species (ROS) and restoring redox balance within cells, as demonstrated in various cellular models [13]. Resveratrol promotes tissue regeneration through its anti-inflammatory and antioxidant activities, as well as by enhancing angiogenesis and collagen deposition [12].

Enzymatic Antioxidants

Superoxide dismutase (SOD), catalase, and glutathione peroxidase are critical components of antioxidant defenses against ROS, which protect the cellular redox state [13]. Superoxide dismutase catalyzes the dismutation of superoxide to hydrogen peroxide, which is further metabolized by catalase and glutathione peroxidase [13].

Antioxidants of Nanomaterials

Cerium oxide (CeO_2) nanoparticles are unique in that they exhibit self-regenerative antioxidant activity, capable of cycling between Ce^{3+} and Ce^{4+} states in vivo, forming oxygen vacancies and storing oxygen to continuously scavenge ROS without being exhausted [14, 16]. They are more effective in acidic conditions, such as those found in chronic wounds [15]. These nanoparticles have been shown to reduce oxidative stress, modulate inflammation regulation, and neovascularization in the diabetic wound models [15, 17, 18].

Advanced Delivery Systems

Antioxidant-loaded hydrogel and nanocomposite dressings facilitate wound infiltration and provide a controlled, sustained release [13]. These can sense environmental cues, such as ROS and pH, to trigger therapeutic release on demand [13].

Pro-oxidant and Regulated ROS Remedies

Controlled ROS Production

Low basal amounts of ROS are also required for healing and signaling pathways involved in cell migration and tissue regeneration [5, 19]. Topical treatment with a low dose of H_2O_2 (~10 mM) is known to promote keratinocyte, fibroblast function, angiogenesis, and the induction of the growth factor cascade [5, 19].

Photodynamic Therapy (PDT)

PDT uses light-sensitive agents, particular wavelengths of light, and molecular oxygen via generating ROS within a given wound site [5, 19]. This facilitates local oxidation reactions which aid an antimicrobial defense and tissue regeneration [5, 20, 21].

Therapeutic Threshold Control

Controlling the OS to the most advantageous level is essential [5]. Smart delivery systems based on wound-responsive cues, such as pH, oxygen, or inflammatory factors, have been developed to actively control the ROS delivery [5].

Strategies of Gene and Molecular Targeting

NADPH Oxidase Modulation

The selective inhibition of NOX enzymes, which are major sources of ROS in immune and vascular cells, may provide specific control of oxidative signaling for each phase and each tissue repair [27].

Signal Pathway Regulation

Redox-sensitive signal cascades, such as hsp70 and jun-1, are strong regulators involved in important regenerative events [5, 19]. Agents such as Resolvin E1 and PDGF also manipulate these pathways for repair promotion [19].

Gene Editing Technologies

CRISPR-Cas and RNAi provide the fine-tuning to ROS-related genes to increase antioxidant defenses and mitigate potential oxidative assaults [19].

Combination Therapies

Multi-Target Strategies

Synergistically, the effects of antioxidants and antimicrobial or growth factors improve the healing process [17, 18]. Nanomaterials incorporated into classical dressings show advantages over monotherapy [17, 18].

Dynamic ROS Modulation

Combining ROS-inducing therapies, such as PDT, with antioxidants permits time-dependent regulation of oxidative activity [5, 21]. Smart biomaterials are a tool to specifically program the nature and time for intervention for each healing phase [5, 21].

Future Perspectives

Novel methods cover not only ROS-sensitive intelligent biomaterials, ROS biomarker-based personalized therapy, but also sophisticated delivery systems such as exosomes [21]. The inclusion/combination with immunomodulation and tissue engineering may change the future of treatment for chronic wounds [21]. Problems to tackle in the future include the exact real-time monitoring and broadening of the clinical validation covering the safety and effectiveness as well [21].

Gaps in the Literature & Future Directions

Despite the progress made, several gaps continue to exist in the knowledge and application of ROS modulation in wound healing. One important limitation is the lack of established criteria for "safe" levels of ROS in wounds. Current estimates for H_2O_2 have varied from 10 µM to over 250 µM but are based on individual reports and vary with tissue type and model system [22].

Additionally, current in vitro and animal models typically do not reflect the full complexity of human chronic wounds. New technologies such as 3D-bioprinted skin, organ-on-chip technology, and chronic wound-mimicking biomaterials are now emerging to provide more reproducible platforms for studies [22].

There have been few large clinical trials that have thoroughly examined ROS-modulating

therapies with long-term follow-up and proper control groups. This paucity of clinical data stands in the way of guidelines development and approval of new drugs [5].
Directions for future research will need to include exploration of gene therapy (e.g., Nrf2 pathways targeting), nanotechnology-delivery platforms (e.g., nanozymes and polymeric carriers), and AI-augmented biosensors for real-time redox status monitoring in wounds. Personalized medicine strategies—based on genetic, metabolic, and environmental considerations—will be essential to the optimization of outcomes and prevention of chronicity in wounds [5].

Molecular Mechanisms and Pathways

Inflammation Phase

ROS Generation and Immune Defense: Immediately after injury, neutrophils and macrophages generate ROS via NADPH oxidase in a respiratory burst, producing O_2^- and H_2O_2. These are essential for killing invading microbes and preventing infection [23, 24].
Leukocyte Recruitment: ROS act as secondary messengers, activating transcription factors such as NF-κB, AP-1, and MAPKs. This leads to the upregulation of pro-inflammatory cytokines (e.g., TNF-α, IL-1β) and adhesion molecules (e.g., P-selectin, ICAM-1), promoting leukocyte migration to the wound site [23, 7].
Chronic Inflammation: By activating the NLRP3 inflammasome and impairing the M1→M2 transition, persistent ROS (>50% above physiological levels) maintain M1 macrophage dominance. These delays wound closure by increasing TNF-α, IL-1β, and MMPs [4, 6, 25].

Proliferation Phase

Angiogenesis: ROS, especially H_2O_2, stabilize HIF-1α and upregulate VEGF, promoting endothelial cell proliferation and new blood vessel formation. This is essential for granulation tissue development and nutrient delivery to the wound bed [7, 24].
Cell Migration and ECM Synthesis: Moderate ROS levels stimulate fibroblast and keratinocyte migration through activation of MAPK and PI3K/Akt pathways, enhancing collagen synthesis and extracellular matrix (ECM) deposition. Controlled ROS facilitate the replacement of damaged tissue with granulation tissue [23, 24].
Oxidative Stress: ROS >20 μM degrade ECM components via MMP-1/9 upregulation and impair collagen cross-linking, weakening granulation tissue [4, 6].

Remodeling Phase

ECM Dynamics: ROS regulate MMP/TIMP balance through AP-1 and NF-κB. Physiological levels facilitate controlled collagen remodeling, while excess ROS cause pathological fibrosis or chronic ulceration [7, 4, 6].
Macrophage Polarization: ROS facilitate M1→M2 transition via Nrf2 activation. Dysregulation stalls this shift, disrupting TGF-β1-mediated myofibroblast differentiation and collagen maturation, contributes to fibrosis or chronic wounds [4, 25].

Signaling Pathways in ROS

NF-κB Pathway

In order to promote pro-inflammatory gene expression, ROS oxidises IκB kinase (IKK) and releases NF-κB. Compared to acute wounds, chronic wounds have 60% greater NF-κB activation, which prolongs cytokine storms [4, 6, 25].

Nrf2/ARE Pathway

ROS triggers Nrf2-Keap1 dissociation, inducing antioxidant genes (SOD, catalase). This pathway is vital for wound re-epithelialization and for protecting against oxidative stress. Oxidative damage is rendered worse by impaired Nrf2 activity (↓40% in diabetic ulcers) [23, 26, 6].

HIF-1α Pathway

ROS stabilize HIF-1α by inhibiting prolyl hydroxylases, which increases VEGF expression and angiogenesis, supporting tissue regeneration [7, 24].

MAPK/PI3K-Akt Pathways

Low H_2O_2 (<10 μM) activates ERK/JNK for cell proliferation and PI3K/Akt for survival. Dysregulation impairs fibroblast and keratinocyte function [7, 6, 25].

Sources of Reactive Oxygen Species (ROS) in Wound Healing

Cellular Sources of ROS

NADPH Oxidase (NOX) Enzymes

NOX isoforms, during different stages of cutaneous wound healing, are important producers of reactive oxygen species (ROS) [27]. During the inflammatory stage of wound healing, NOX enzymes have a crucial role in the activation of immune cells as well as defense mechanisms against microbes [27]. Additionally, cell signaling, removal of pathogens and tissue remodeling are dependent on ROS generation managed by NOX enzymes [27].

Mitochondrial ROS Production

An important intracellular generator of ROS is mitochondria, which is done through a number of processes [32]. Mitochondrial fragmentation is part of the response to injury which modifies the signaling patterns of ROS [32]. When the structure and function of mitochondria are damaged, more superoxide is produced by the electron transport chain [5]. During tissue repair, the fate of the cell can be affected by the production of mitochondrial ROS which is particularly important during responses to cellular stress [32].

Mitochondria can be found in almost every type of cell that are involved in wound healing such as keratinocytes, fibroblasts, endothelial cells, and immune cells [32]. When the processes of mitochondria and ROS signaling are combined, a feedback loop is created which can lead to apoptosis or promote the survival or proliferation of the cells depending on the severity of oxidative stress [32].

Immune Cell-Derived ROS

Inflammatory cells, particularly neutrophils and macrophages, produce ROS during antibacterial defense and clearance of tissues [27, 28]. ROS is produced by neutrophils through NOX dependent and NOX independent mechanisms which creates an environment which assists with pathogen and debris removal [27]. Macrophages also take part in the resolution of inflammation and remodeling of tissues by producing ROS [27, 28].

Pathological Sources and Complications

Bacterial Biofilms

A pathological source of ROS are bacterial biofilms which can be found in chronic wounds such as diabetic wounds [30]. They interrupt with the natural healing process of the body by creating a cycle of oxidative stress through the constant production of ROS [30]. Interactions between the immune response of the host and bacterial metabolism results in the production of ROS which delays the healing of wounds and causes chronic inflammation, overpowering the antioxidant defenses of cells [30].

Prostaglandin E2-Mediated ROS Generation

ROS mediates the production of prostaglandin E2 through a specific pathway as a result of epithelial injury [29]. This biological mechanism connects early tissue injury to persistent inflammatory reactions by using ROS dependent signaling cascades; however, if the PGE2-ROS axis isn't regulated, it might lead to chronic wounds [29].

Tissue-Specific ROS Sources

Hepatic Wound Healing and Fibrogenesis

Some redox processes support fibrogenesis and chronic wound healing in hepatic tissue repair [31]. In contrast to the healing of cutaneous wounds, the liver produces noticeable patterns of ROS generation through its high metabolic activity and detoxifying processes [31]. ROS is mainly produced by the hepatic Kupffer cells and stellate cells during the damage and repair of the liver but it may impair the progress of fibrosis [31].

Epithelial Cell Sources

During the re-epithelialization of wounds, epithelial cells, especially keratinocytes, participate in the formation of ROS through multiple routes [27, 29]. These epithelial cells produce ROS through growth factors, mechanical stress and intercellular signalling molecules [29]. During wound healing, the maintenance of the equilibrium between cell differentiation and proliferation is dependent on ROS production by epithelial cells [29].

Molecular Mechanisms of ROS Generation

Cellular and molecular pathways which lead to ROS generation in wound healing involve both enzymatic and non-enzymatic processes [28]. At multiple stages of wound healing, the formation of ROS is controlled by specific molecular pathways and this shows how normal wound healing physiology involves oxidative stress mechanisms [28].

CONCLUSION

Reactive oxygen species (ROS) are key figures in the primary process of wound healing with the characteristic of bipolarity in the aspect of their function where limited numbers can promote hemostasis, inflammation, proliferation, and remodeling but ROS overload leads to oxidative damage and tissue repair can be interrupted or derailed [4-7]. Emerging therapeutic strategies, from antioxidant delivery systems to ROS-generating therapies like photodynamic therapy, emphasize the clinical need for selective redox modulation [5, 13, 19, 20]. Conquering the vitro promise vs. in vivo heterogeneity gap remains a challenge, as does determining therapeutic ROS thresholds [5, 9, 22]. Therapeutic strategies targeting redox-directed and personalized approaches aided by immediate biomarker detection and combined drug delivery systems promise to be the best make-up of wound-healing programs of both acute injuries and chronic conditions [5, 10, 21].

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