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REVIEW

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Oxidative stress following spinal cord injury: From molecular mechanisms to therapeutic targets

Mengsi Yu[1] | Zhiying Wang[1] | Dongmin Wang[2] | Milikemu Aierxi[1] | Zhanjun Ma[3] | Yonggang Wang[1,4]

[1]The Second Clinical Medical College, Lanzhou University, Lanzhou, China

[2]Medical College of Northwest Minzu University, Lanzhou, China

[3]Louvain Drug Research Institute, Advanced Drug Delivery and Biomaterials, Université Catholique de Louvain, UCLouvain, Brussels, Belgium

[4]Department of Orthopedics, Lanzhou University Second Hospital, Lanzhou, China

Correspondence
Zhanjun Ma, Louvain Drug Research Institute, Advanced Drug Delivery and Biomaterials, Université Catholique de Louvain, UCLouvain, Brussels 1200, Belgium.
Email: zhanjun.ma@uclouvain.be

Yonggang Wang, Department of Orthopaedics, Lanzhou University Second Hospital, No.82 Cuiyingmen Street, Lanzhou, Gansu 730030, China.
Email: wangyg18@lzu.edu.cn

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Abstract

Spinal cord injury (SCI) is a medical condition that results from severe trauma to the central nervous system; it imposes great psychological and economic burdens on affected patients and their families. The dynamic balance between reactive oxygen species (ROS) and antioxidants is essential for maintaining normal cellular physiological functions. As important intracellular signaling molecules, ROS regulate numerous physiological activities, including vascular reactivity and neuronal function. However, excessive ROS can cause damage to cellular macromolecules, including DNA, lipids, and proteins; this damage eventually leads to cell death. This review discusses the mechanisms of oxidative stress in SCI and describes some signaling pathways that regulate oxidative injury after injury, with the aim of providing guidance for the development of novel SCI treatment strategies.

KEYWORDS
apoptosis, inflammatory reaction, oxidative stress, reactive oxygen species, signal pathway, spinal cord injury

1 | INTRODUCTION

Spinal cord injury (SCI) is a medical condition that results from severe trauma to the central nervous system (CNS), it leads to nerve cell death and conduction pathway disruption, as well as losses of motor and sensory function below the plane of injury, with the potential for paralysis and death. SCI imposes great economic and psychological burdens on affected patients and their families. Epidemiological surveys have suggested that the annual incidence of SCI is 40–80 per 1 million population (Kumar et al., 2018) and the cost of caring for SCI patients is $10 billion per year (Thompson et al., 2015), there are significant differences in morbidity, mortality, patient age, sex, etiology, and injury severity between developed and developing countries. The annual incidence and prevalence of traumatic SCI are higher in the United States (i.e., incidence of 54 cases per 1 million population [Kumar et al., 2018]) than in other parts of the world. SCI is mainly attributed to traumatic factors, including violence, extreme sports, and traffic accidents; notably, traffic accidents are the most common cause of SCI, followed by falls among older adults. Currently, many SCI patients are between 16 and 30 years of age in most regions and countries worldwide (Singh et al., 2014).

Mengsi Yu and Zhiying Wang contributed equally to this study and share first authorship.

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Despite several decades of SCI research worldwide, the most common treatments (e.g., spinal cord decompression, glucocorticoid shock therapy, rehabilitation exercise, and nutritional neurodrugs) are inefficient and only provide short-term improvement (Khorasanizadeh et al., 2019), they inevitably leave survivors with long-term severe nerve injury. In recent years, strategies for the treatment of SCI have mainly focused on secondary injury prevention, preservation of residual axons at the site of injury, reconstruction of interrupted nerve conduction pathways, and restoration of nerve conduction function above and below the plane of injury (e.g., by promoting nerve regeneration and repair, along with protection of injured nerves). However, there is limited capacity for axon regeneration; this process strongly depends on the spinal cord microenvironment after SCI. Thus, there is an urgent need for novel SCI treatment strategies with greater efficacy.

Because of the transient hypoxia caused by bleeding and vascular stretching in the spinal cord, initial hypoxic injury can trigger oxidative stress events through inflammatory responses that involve hyperactive neurons and glutamate excitotoxicity after SCI. The systemic antioxidant capacity is insufficient under conditions of oxidative stress; this leads to excessive reactive oxygen species (ROS) production and the potential for additional damage (Gao et al., 2019). ROS cause various types of damage, including lipid peroxidation, DNA damage, and cell death. Hall (2011) suggested that free radical generation during the acute phase of SCI is the main cause of secondary neuronal cell necrosis. Antioxidant therapy can reduce acute oxidative stress injury, thereby facilitating the improvement and recovery of neurological function after SCI (Shimizu et al., 2018; Zhou et al., 2018). Accordingly, methods to prevent oxidative stress after SCI or reduce the extent of injury have been suggested as potential SCI treatment strategies. This review focuses on the role of oxidative stress in SCI pathogenesis and considers SCI treatment via oxidative stress reduction.

2 | PATHOPHYSIOLOGY AFTER SCI

Acute SCI usually occurs because of sudden trauma to the spine and results in fractures and vertebral dislocations. SCI typically involves two mechanisms, primary (mechanical) injury and secondary injury (Figure 1). The primary injury is irreversible, usually due to external mechanical forces leading to compromised spinal integrity and direct neuronal damage and characterized by bone fragments and spinal ligament tears (Anjum et al., 2020). Secondary injury is the inflammation and cell death in the injury microenvironment caused by a series of cells and cytokines based on primary injury (Xia et al., 2023). The main determinants of SCI severity are the extent of the initial disruption and the duration of spinal cord compression. The occurrence of biochemical, mechanical, and physiological changes in neural tissue activates a cascade of events associated with secondary injury. Although the clinical picture suggests complete loss of function, in the primary SCI stage, very few parts are still connected by some axons, thus reflecting an incomplete and partial injury state (Dimitrijevic et al., 2015).

Significance

SCI is a medical condition that results from severe trauma to the central nervous system; it imposes great psychological and economic burdens on affected patients and their families. High levels of ROS can cause irreversible oxidative damage to macromolecules, (e.g., nucleic acids, lipids, and proteins) and interactions with inflammatory responses, cellular autophagy, and apoptosis; these processes can lead to a complex cascade of secondary damage. This review discusses the mechanisms of oxidative stress in SCI and describes some signaling pathways that regulate oxidative injury after injury, with the aim of providing guidance for the development of novel SCI treatment strategies.

2.1 | Primary injury

Primary injury (generally within 2 h) is irreversible and related to mechanical injury of the spine after direct or indirect external impact; fracture or vertebral dislocation is the main manifestation (Fehlings et al., 2017). Spinal cord compression with tearing or shearing leads to axonal rupture, vascular supply interruption, hypotension/hyperperfusion, and edema formation (Anjum et al., 2020). The presence of a hematoma in the medulla (mainly in the gray matter) and ischemia in the corresponding spinal cord region (at sites of more severe hemorrhage) suggests that hemorrhage leads to secondary ischemia. Because half of the white matter in the spinal cord is supplied by arteries that branch from the sulcus arteriosus through the gray matter, a gray matter hematoma can lead to ischemia in the surrounding white matter. Additionally, substantial thromboxane A_2 production after SCI causes spasmodic constriction of spinal microvasculature and reduction of microcirculatory blood flow. Moreover, thromboxane A_2 promotes platelet adhesion and aggregation, as well as the release of adenosine diphosphate and 5-hydroxytryptamine; these changes promote vasoconstriction and subsequent microthrombus formation or embolism in spinal vessels (Kanda et al., 2013).

2.2 | Secondary injury

Secondary injury is characterized by a series of cellular and molecular changes that begin within minutes of the primary injury. The secondary injury consists of three consecutive and overlapping phases: acute (within 48 h after injury), subacute (48 h to 2 weeks after injury), and chronic (up to 6 months after injury) (He et al., 2022). Secondary injury usually worsens the injury and causes permanent harm to the patient (Xia et al., 2023).

After primary injury, secondary vasogenic edema occurs along with ionic imbalance, lipid peroxidation, and glutamate excitotoxicity. Macrophage and lymphocyte infiltration occurs, inducing an inflammatory response and further oxidative stress. This progressive amplification of pathophysiological responses leads to impaired

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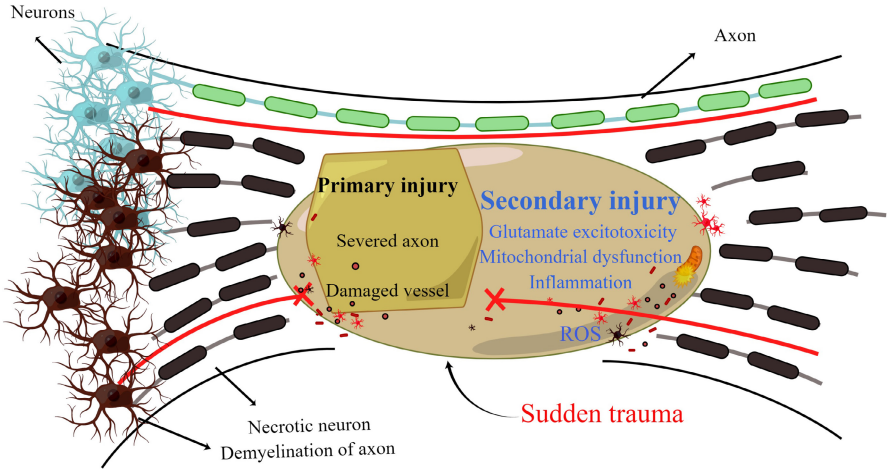


FIGURE 1 Pathophysiology of SCI. Mechanical injury to the spine after direct or indirect external impact results in axonal rupture, disruption of spinal vascular supply, and hypotension/hypoperfusion. Secondary injuries occur in conjunction with primary injuries. The main pathophysiological changes are manifested by spinal cord vascular ischemia, inflammatory responses, neuroexcitotoxic responses, and free radical production; these processes lead to nerve cell death.

neuronal homeostasis and secondary injury (Alizadeh et al., 2019). After SCI, substantial leukocyte infiltration and accumulation occur in the injured segment of the spinal cord; this accumulation peaks at 3 h after injury. The activated leukocytes release large amounts of cytokines (e.g., tumor necrosis factor, elastase, and ROS) that cause vascular endothelial damage and blood flow stagnation (Vanzulli & Butt, 2015). In addition, the initial reactive ischemia and hypoxia after SCI can affect mitochondrial electron transfer, leading to free radical production. Subsequently, hemorrhage occurs in central gray matter of the spinal cord, releasing iron and copper ions into the interstitial space; these ions can catalyze the Fenton reaction, thus generating large amounts of hydroxyl radicals ($\cdot OH^-$) and the onset of lipid peroxidation (Fan et al., 2016).

Glutamate is the main excitatory neurotransmitter in the mammalian nervous system; it acts via glutamate receptors to mediate neuronal damage and cause excitotoxicity. Wu et al. (Wu et al., 2004) reported that extracellular glutamate and aspartate levels significantly increase in the immediate postinjury period (approximately 10 min) after CNS trauma. The excitotoxic process is accompanied by excessive inward flow of Ca^{2+} ions, which eventually leads to excessive intracellular Ca^{2+} accumulation. After SCI, large amounts of Ca^{2+} ions flow inward; intrasynaptic Ca^{2+} accumulation and extracellular Ca^{2+} reduction begin 30 min after injury and reach a peak at 8 h. The Ca^{2+} level can remain elevated at 1 week after injury. Excess Ca^{2+} accumulation in cells results in the overactivation of phospholipases, acetal phospholipases, calcium-activated proteases, protein kinases, guanylate cyclase, nitric oxide synthases, calcium-regulated phosphatases, and nucleic acid endonucleases, this activation can cause excessive production of toxic reaction products (e.g., ROS) (Alizadeh et al., 2019). In addition, the disruption of Na^+ and K^+ ion homeostasis because of changes in cell membrane structure after injury leads to cell membrane depolarization, ATPase failure, and further elevation of intracellular Ca^{2+}, these changes exacerbate the oxidative stress-related injury.

After SCI, resident microglia in the spinal cord are activated, while rapidly infiltrating leukocytes begin to release large quantities of inflammatory cytokines and ROS; these factors promote nerve cell necrosis and lysis, along with injury exacerbation (Silva et al., 2014). Apoptosis and necrosis occur concurrently within 24 h after SCI, while apoptosis is predominant after 24 h; this leads to greater CNS damage. Glial cell apoptosis appears at various stages from 4 h to 14 d after injury, the first peak (at 24 h) involves the spread of apoptosis from the center of the injured area into the surrounding area, while the second peak (at 7–10 d) mainly consists of oligodendrocyte apoptosis. Oligodendrocytes are presumed to constitute most of the apoptotic cells after SCI. Oligodendrocytes wrap around axons to form myelin sheaths, and axonal demyelination is caused by extensive oligodendrocyte death (Nickel & Gu, 2018); this process affects residual nerve function and leads to further nerve tissue deterioration.

In the chronic secondary injury phase of SCI, glial scar cysts are caused by white matter demyelination; gray matter lysis; connective tissue deposition; and the proliferation of reactive astrocytes, microglia/macrophages, and extracellular matrix. Continued enlargement of the lesion site and cyst formation are characteristic of SCI in the chronic phase (Alizadeh et al., 2019; Tran et al., 2018). In approximately one-third of SCI patients, cyst formation leads to spinal cord cavitation that gradually progresses and inhibits axonal regeneration, limited remyelination of oligodendrocytes and Schwann cells may be predictive of slightly improved function during this period (Alizadeh et al., 2015; Fan et al., 2018; Pukos et al., 2019).

3 | MECHANISM OF OXIDATIVE STRESS INJURY AFTER SCI

Oxidative stress is a series of adaptive responses caused by an imbalance between ROS levels and the antioxidant system; these responses lead to the accumulation of excess free radicals (e.g., ROS

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and reactive nitrogen species [RNS]) and subsequent cytotoxic effects (Sies & Jones, 2020). Oxidative stress itself is a fundamental protective mechanism during normal physiological activity; it helps to regulate processes such as cell signaling, cell proliferation, and apoptosis. The production of ROS (e.g., superoxide radicals [$O_2^{\cdot-}$] and hydroxyl radicals [$\cdot OH^-$]) and RNS (e.g., nitric oxide [$\cdot NO^-$]) increases throughout the body under conditions of oxidative stress. SCI is accompanied by excessive free radical production, the degree of oxidation exceeds the normal systemic scavenging ability, which leads to the initiation of an oxidative emergency reaction. In addition, oxidative stress is associated with secondary events (e.g., inflammatory responses, excitotoxicity, and neuronal and glial cell apoptosis) after primary injury. The spinal cord is particularly sensitive to ROS-induced lipid peroxidation because of its high polyunsaturated fatty acid content, this lipid peroxidation results in excessive antioxidant depletion in tissues. Therefore, the spinal cord is vulnerable to oxidative damage. Numerous experimental and clinical studies have confirmed the importance of ROS and lipid peroxidation in SCI pathogenesis. Methods to prevent oxidative stress or reduce the extent of damage by targeting the mechanisms of oxidative stress may be useful for SCI treatment (Figure 2).

3.1 | Overload of ROS generation

ROS are oxygen-containing substances with high reactivity; they are mainly produced by redox reactions during normal physiological activity. ROS and RNS are major drivers of oxidative damage to proteins, lipids, and nucleic acids; they induce inflammation, autophagy, apoptosis, and blood–brain barrier disruption (Zhang, Xu, et al., 2019). When combined with an additional electron, molecular oxygen (O_2) becomes an anion with an unpaired electron; this is referred to as the superoxide radical ($O_2^{\cdot-}$). In the cytoplasmic matrix, $O_2^{\cdot-}$ exists in equilibrium with the hydroperoxyl radical ($HO_2^{\cdot-}$): $O_2^{\cdot-} + H^+ \rightarrow HO_2^{\cdot-}$.

$HO_2^{\cdot-}$ is extremely lipid soluble and is a potent reducing agent. In the presence of intracellular oxidases, $O_2^{\cdot-}$ is a byproduct of the biological oxidation that occurs during mitochondrial respiration (Vaziri et al., 2004). In most cells, the electron transport chain consumes 90% of cellular oxygen; 2% of the oxygen is converted to oxygen radicals in the mitochondrial inner membrane and matrix (Chen et al., 2021; Muller et al., 2004). RNS consist mainly of peroxynitrite ($ONOO^-$), which is produced by the reaction of $\cdot NO^-$ radicals with $O_2^{\cdot-}$; this is catalyzed by nitric oxide synthase ($O_2^{\cdot-} + \cdot NO^- \rightarrow ONOO^-$). In an acidic environment, peroxynitrous acid (ONOOH) is readily protonated and cleaved to produce extremely reactive nitrogen oxide radicals ($\cdot NO_2^-$) and $\cdot OH^-$: ($ONOOH \rightarrow \cdot NO_2^- + \cdot OH^-$). In particular, peroxynitrite ($ONOO^-$) can react with CO_2 to form nitrocarbon peroxide ($ONOOCO_2$), which decomposes into $\cdot NO_2^-$ and carbonate radicals ($CO_3^{\cdot-}$): ($ONOOCO_2 \rightarrow \cdot NO_2^- + CO_3^{\cdot-}$). During the first minutes or hours after SCI, peroxidative stress occurs when the $O_2^{\cdot-}$ generated by various pathways exceeds the scavenging capacity of superoxide dismutase (SOD) because of low catalase, SOD, and glutathione peroxidase activities (i.e., enzymes responsible for scavenging free radicals in the CNS [Heo & Lee, 2004]); thus, the CNS becomes more sensitive to oxidative stress and excess superoxide radicals can cause greater damage.

Under normal conditions, the $O_2^{\cdot-}$ produced by physiological processes is rapidly removed by enzymatic antioxidant systems (SOD, catalase, selenium glutathione peroxidase, selenium-free glutathione peroxidase, glutathione sulfotransferase, and aldo-keto reductase; all are self-generated antioxidant enzymes) and nonenzymatic antioxidant systems (antioxidants). However, under pathophysiological conditions in SCI, the immune system is activated and neutrophils

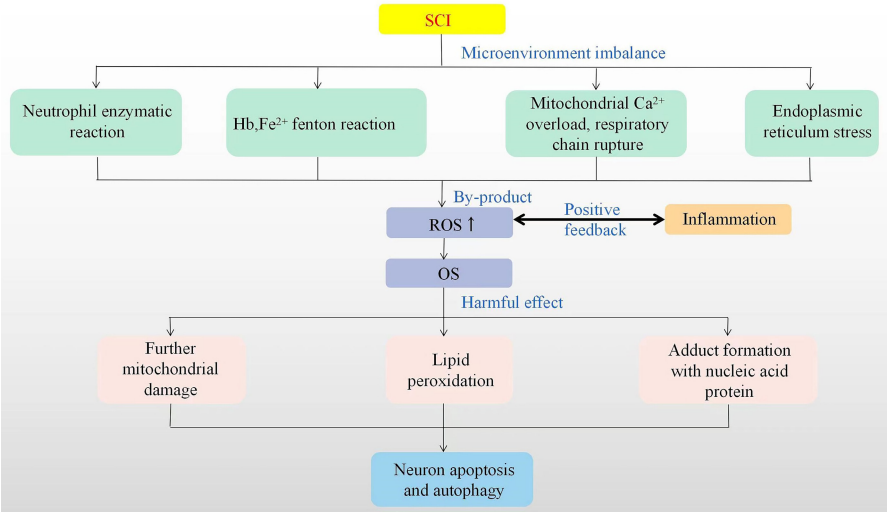


FIGURE 2 Mechanisms of oxidative stress injury after SCI. After SCI, activated neutrophils, phagocytes, mitochondria, endoplasmic reticulum, and lysed red blood cells (Fe^{2+}) all contribute to excessive release of ROS. Oxidative stress damage occurs when ROS release exceeds the scavenging capacity. The increased levels of ROS induce lipid peroxidation, protein and DNA damage, and inflammatory response crosstalk, leading to further exacerbation of SCI.

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are the first inflammatory cells to reach the injured spinal cord (Orr & Gensel, 2018); the neutrophil count peaks at 24 h after injury. The release of chemokines and cytokines, along with upregulation of various adhesion molecules on endothelial cells, attracts neutrophils and monocytes to the site of injury. Their main functions are phagocytosis and debris removal; the secretion of proteases, elastase, and myeloperoxidase; and release of ROS. In addition to neutrophils, microglia are activated immediately after SCI; they exhibit altered cell morphology and protein expression profiles, along with localization to the site of injury. These activated microglia closely resemble circulating macrophages in terms of morphology, protein expression profile, and function (Aschauer-Wallner et al., 2021; David & Kroner, 2011). Rapidly increasing macrophages produce large amounts of $O_2^{\cdot-}$ through the activity of nicotinamide adenine dinucleotide phosphate oxidase (NOX) (Zhang et al., 2016). Furthermore, infiltrating macrophages deliver protein hydrolases, ROS, and inflammatory cytokines to the injury microenvironment. CNS cells have been reported to contain large amounts of phosphoramidated adenine dinucleotides [NAD(P)H]; the oxidation of NAD(P)H in these cells is a major source of $O_2^{\cdot-}$ production (Zia et al., 2009).

Iron has crucial roles in CNS metabolic processes, including oxidative phosphorylation, myelin synthesis, and neurotransmitter production (Smith et al., 2013). Under normal physiological conditions, iron is present in complexes with ferritin and transferrin. After SCI, the tissue pH is greatly reduced in the damaged area; ferric ions are readily released from ferritin and transferrin, $O_2^{\cdot-}$ is produced by the Fenton reaction in the presence of ferrous ions, and $\cdot OH^-$ is formed (Zhang, Xu, et al., 2019). Ferritin and transferrin-bound iron can also be detached from protein by $O_2^{\cdot-}$ reduction. In addition, the iron released from hemoglobin during SCI bleeding catalyzes $\cdot OH^-$ production from H_2O_2 (Sadrzadeh & Eaton, 1988).

The mitochondrial respiratory chain is widely regarded as the main source of ROS in cells. However, as the main site of ROS generation, mitochondria are able to initiate and regulate autophagy (Chen et al., 2021). Mitochondria regulate cytosolic calcium levels and have an important role in calcium-dependent neuronal cell death (Turtle et al., 2019). Under physiological conditions, the energy-dependent Ca^{2+} buffering system within axons removes excess Ca^{2+}. When adenosine triphosphate (ATP) is depleted by excessive demand for demyelination after SCI, the standard Ca^{2+} buffering fails and intracellular Ca^{2+} levels rise (Plemel et al., 2014); this results in the activation of complex-1 (NADH), followed by increased ATP production and enhanced ROS production (Anjum et al., 2020). Next, high levels of ROS increase the mitochondrial membrane permeability, causing pores to form on the mitochondrial surface (Xiong & Hall, 2009). The opening of these pores causes an overload of mitochondrial Ca^{2+}, leading to a decrease in mitochondrial membrane potential, damage to mitochondria, and breakdown of the mitochondrial respiratory chain. These processes result in further release of excess ROS (Malecki et al., 2000). Chronic impairment of mitochondrial function leads to substantial ROS production, initiation of mitochondrial self-clearance signals, and induction of mitochondrial autophagy (Filomeni et al., 2015). In addition, the disulfide bonds of proteins translated in the endoplasmic reticulum (ER) are extremely sensitive to changes in redox homeostasis; glutamate excitotoxicity and inflammatory responses during SCI can lead to ER stress, resulting in protein misfolding, abnormal protein accumulation, and Ca^{2+} imbalance (Jiao et al., 2020). During oxidative protein folding, protein disulfide isomerase accepts electrons from the protein folding substrate, thus oxidizing thiol groups on cysteine residues and forming disulfide bonds (Cao & Kaufman, 2014). Endoplasmic reticulum oxidase 1α (ERO1α) accepts electrons from protein disulfide isomerase, then transfers them to molecular oxygen; this leads to ROS production. ROS act as signaling intermediates to alleviate ER stress via periodic responses. In the presence of continued ER stress, delayed expression of proteins (e.g., C/EBP homologous protein) leads to further elevation of ROS levels (Ochoa et al., 2018). In the ER, Ca^{2+} transfer at ER–mitochondria contact points leads to mitochondrial dysfunction, which increases mitochondrial ROS production and results in cellular oxidative damage or neuronal cell death.

3.2 | Oxidative stress-mediated damage to biological macromolecules

The CNS is characterized by high metabolic activity and high oxygen demand, both of which facilitate free radical formation (Magistretti & Allaman, 2015). The CNS also has weak antioxidant defenses (Cobley et al., 2018; Salim, 2017). In the presence of oxidative stress, high ROS levels can result in irreversible oxidative damage to macromolecules, including nucleic acids, lipids, and proteins. Oxidative stress causes neuronal damage through three basic pathways: attacks on mitochondrial membranes and mitochondrial DNA close to their formation sites, leading to mitochondrial dysfunction and increased ROS production; interactions of ROS with cell membrane lipids, resulting in lipid peroxidation (this produces structural changes and dysfunction involving organelles and cell membranes) (Catalá & Díaz, 2016); and interactions of ROS with nuclear DNA and proteins, thereby causing base modifications and DNA breaks, protein breaks, or degradation (this results in DNA damage and abnormal protein function).

Oxidative damage to biomolecules (e.g., lipids, nucleic acids, and proteins) by oxidative stress directly causes neuronal cell damage and apoptosis.

3.2.1 | Lipid peroxidation

The CNS is particularly sensitive to oxidative stress because it contains high levels of peroxidation-sensitive lipids (e.g., arachidonic, linoleic, and docosahexaenoic acids); SCI can lead to substantial release of free fatty acids, especially arachidonic acid, from cell membranes (Toborek et al., 1999). Lipids can be oxidized by extremely lipophilic ROS to form water and unstable lipid peroxyl radicals, which can then combine with other fatty acids to form lipid hydroperoxides and other lipid radicals, self-reactions are also possible. A lipid radical formed in

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the previous stage can react with oxygen to form another lipid peroxyl radical, thereby causing a chain reaction of lipid peroxidation (Catalá & Díaz, 2016). The major products of lipid peroxidation, malondialdehyde (MDA), and 4-hydroxynonenal/4-hydroxy-2-nonenal (HNE), are regarded as markers of oxidative stress after SCI (Ayala et al., 2014; Barrera et al., 2008). In contrast to ROS, these products lack an electrical charge and thus can easily pass through the cell membrane and migrate to the cytoplasm (Jaganjac et al., 2021; West et al., 2010), this passage allows them to cause damage both inside and outside of cells. HNE and MDA may modify amino acid residues to form stable adducts that can cause protein damage (Darmanis et al., 2015). As major components of biological membranes, lipids are critical roles for maintaining structural integrity in cells and organelles. The main intermediates of these reactions are lipid hydroperoxides, which disrupt membrane structure; peroxidation alters lipid–lipid interactions, membrane permeability, ionic gradients, membrane fluidity, and membrane permeability (Del Rio et al., 2005). Consequently, ROS-mediated lipid peroxidation is increasingly recognized as an important factor in oxidative neuronal cell death after SCI.

3.2.2 | Protein damage

Proteins are major components of biological systems; they comprise 70% of the dry mass of cells and tissues. ROS can cause protein misfolding, which leads to altered protein function, chemical fragmentation, or increased susceptibility to proteolytic attack (Dröge, 2002). Phosphorylated Tau protein (p-Tau) was reportedly elevated by twofold in damaged axons on the cephalic and caudal sides at 4 h after severe SCI; cysteinase-3 was activated by cytochrome C complexes released from damaged mitochondria in axons, which also cleave Tau; and excessive loss of microtubule-bound Tau led to the depolymerization of microtubule structures and subsequent damage to axonal transport (Caprelli et al., 2019). Proteolysis may be increased by >11-fold after exposure to superoxide or hydrogen peroxide (Davies & Goldberg, 1987). Free radical-mediated damage can be detected in the peptide backbone, and most free radicals react with proteins through three main pathways: extraction of hydrogen atoms from C–H, S–H, N–H, or O–H bonds, extraction of electrons from electron-rich positions, and addition to electron-rich centers (aromatic rings and sulfur species) (Hawkins & Davies, 2001, 2019). Highly reactive radicals (e.g., $\cdot HO^{-}$) have minimal selectivity and thus react with diverse electron-rich sites, which leads to damage in various amino acid side chains, reactions are pH dependent, such that higher pH causes faster oxidative damage (Davies, 2016). In a particular signaling protein, oxidative stress can lead to loss of function, gain of function, or conversion to a different function.

3.2.3 | DNA damage

Alkaline single-cell gel assays in SCI rats revealed increased numbers of DNA breaks in blood cells, hepatocytes, and kidney cells; thus, SCI induced genomic damage in multiple organs in those rats (Medalha et al., 2012). Oxidative stress damage after SCI is a main source of DNA damage (Cooke et al., 2003); it can directly or indirectly modify DNA, thereby affecting cell viability. Hydroxyl radicals can directly attack the DNA backbone by producing oxidative damage, such as oxidized bases, deacylation sites, DNA–DNA intrastrand adducts, single-strand breaks, double-strand breaks, and DNA–protein crosslinks (Chatgilialoglu et al., 2021; Neeley & Essigmann, 2006). Among the known nucleobases, guanine is the most sensitive to ROS because of its low redox potential; the main products of its oxidation are 8-hydroxyguanine and 8-hydroxydeoxyguanosine. Mitochondrial DNA is generally susceptible to oxidative damage because of its proximity to sites of ROS production and its reduced repair capacity compared to nuclear DNA (Kashfi et al., 2021). Therefore, 8-hydroxyguanine and 8-hydroxydeoxyguanosine tend to accumulate under conditions of oxidative damage; they are frequently used as markers of DNA damage. In addition, RNS can cause DNA damage and are considered potentially mutagenic (Xiong & Hall, 2009); they induce nitration, nitrosylation, and deamidation of DNA bases (Turtle et al., 2019).

4 | ROLES OF KEY SIGNALING PATHWAYS IN THE REGULATION OF OXIDATIVE DAMAGE AFTER SCI

Many studies have demonstrated the complexity of the SCI microenvironment; it affects multiple signaling pathways involved in the regulation of oxidative stress and can provide insights for research regarding SCI repair (Schieber & Chandel, 2014).

4.1 | Nuclear factor erythroid 2-related factor 2 signaling pathway

Nuclear factor erythroid 2-related factor 2 (Nrf2) is a core transcription factor in the antioxidant pathway; it plays an important role in the cellular antioxidant defense system by upregulating the expression levels of antioxidant enzymes (Chen et al., 2017; Kura et al., 2020; Weisberg et al., 2003). Binding of the C-terminal region of Kelch-like ECH-associated protein 1 (Keap1) to the Neh2 region of Nrf2 under physiological conditions anchors Nrf2 to the cytosol via cytoplasmic actin. In the cytosol, Nrf2 is rapidly degraded by ubiquitination, such that only a small fraction of the initial protein can enter the nucleus to initiate transcriptional activity by binding to the antioxidant response element (ARE), this regulatory mechanism maintains low transcript levels of genes with AREs (Yamamoto et al., 2018). Under conditions of oxidative stress, the hydrophobic group (–SH) at the Keap1 site loses electrons to a disulfide bond (–S–S–) and dissociates from Nrf2. Subsequently, Nrf2 enters the nucleus to form a heterodimer with Maf protein; this heterodimer recognizes and binds to the ARE (Liu et al., 2018), thus initiating the transcription and expression of downstream target genes (e.g., heme oxygenase-1, glutamate cysteine ligase, glutathione-S-transferase,

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quinone oxidoreductase-1, and SOD) that mitigate oxidative stress, inhibit inflammatory damage, and have antiapoptotic effects (Figure 3). Elevated levels of Nrf2/HO-1 signaling pathway-related proteins cause reduced expression of inflammatory vesicle NOD-like receptor family pyrin domain-containing 3 (NLRP3), this reduced expression of NLRP3 avoids inflammatory responses and apoptosis via recruitment of interleukin (IL)-1 precursors and Caspase-1 (Yan et al., 2019). Nevertheless, endogenous Nrf2-ARE and its activated downstream molecules are unable to protect against the neurovascular impairment and oxidative damage caused by SCI. Moreover, Nrf2 inhibitors significantly increase the levels of inflammatory vesicles and exacerbate cellular damage (Elmarakby & Sullivan, 2012). Thus, there is considerable research interest in the use of exogenous drugs to activate Nrf2-associated pathways for SCI treatment.

4.2 | NF-κB pathway

After SCI, stress and proinflammatory factors (e.g., hemorrhage, ischemia, and hypoxia) activate IκB kinase and cause IκB phosphorylation; this activates the nuclear factor (NF)-κB signaling pathway and regulates oxidative stress by increasing the expression levels of antioxidant proteins, such as manganese superoxide dismutase, glutathione peroxidase, heme oxygenase, and inducible nitric oxide synthase (iNOS) (Morgan & Liu, 2011). Glutathione peroxidase-1, a cytoplasmic enzyme that uses glutathione (GSH) to catalyze the conversion of hydrogen peroxide (H_2O_2) to water, is one of the most important antioxidant proteins upregulated by NF-κB in response to oxidative stress. Manganese superoxide dismutase is a mitochondrial enzyme that protects cells from oxidative stress by converting $O_2^{\cdot-}$ to H_2O_2 (Djavaheri-Mergny et al., 2004), this enzyme is a predicted NF-κB target with antioxidant activity. The ferritin heavy chain is the second-best characterized nuclear factor-κB target

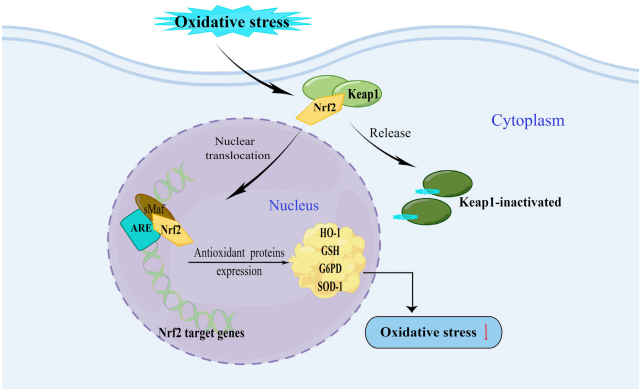


FIGURE 3 Nrf2 signaling pathway. Keap1 protein normally binds and stabilizes Nrf2 in the cytoplasm. After SCI, the Nrf2 bound to Keap1 is activated by ROS, dissociates from Keap1, and translocates to the nucleus where it binds to the AREs; this binding interaction enhances antioxidant capacity and reduces ROS production by upregulating the expression levels of downstream target genes to mitigate the cytotoxic effects of oxidative stress.

(Pham et al., 2004). As an iron storage protein, ferritin heavy chain does not directly scavenge ROS, it protects cells from oxidative damage by preventing iron-mediated Fenton reactions that generate extremely reactive $\cdot OH^-$ radicals. In addition, iNOS is a downstream signaling molecule in the NF-κB pathway; NF-κB induces high levels of iNOS expression, which produces high concentrations of $NO^{\cdot-}$ (Fan et al., 2020), induces cell damage and lipid peroxidation (Jiang et al., 2014), increases vascular permeability, and causes edema. Many enzymes that utilize heme repair groups in catalysis are inactivated by $NO^{\cdot-}$ (Dröge, 2002). Advanced oxidative protein products are the products of oxidative stress that occurs when plasma proteins are attacked by oxygen free radicals, they can be used as biomarkers of oxidative stress in many neuroinflammatory diseases. Advanced oxidative protein products are involved in secondary SCI through regulation of the mitogen-activated protein kinase (MAPK)–NF-κB signaling pathway and activation of microglia; these activities induce neuroinflammation after SCI (Yuan et al., 2019). Moreover, abnormal activation of NF-κB has been demonstrated in neurons and glial cells after SCI; this activation results in upregulation of NF-κB-dependent proinflammatory cytokines and chemokines, which promote inflammatory cell infiltration, neuronal apoptosis, and glial scar formation, thus hindering functional recovery and exacerbating SCI (Filippone et al., 2020; Murphy, 2009). ROS frequently stimulate the NF-κB pathway in the cytoplasm but inhibit NF-κB activity in the nucleus (Kabe et al., 2005). Overall, ROS interact in multiple ways with the NF-κB signaling pathway.

4.3 | Pentose phosphate pathway

The oxidative pentose phosphate pathway (oxPPP) is a fundamental pathway of glucose metabolism involved in nucleotide biosynthesis and cellular reduction/oxygenation (redox) homeostasis (Bonvento & Bolaños, 2021; Hurbain et al., 2022). Its role is prominent following an oxidative stress to metabolize glucose-6-phosphate (G6P) and generate nicotinamide adenine dinucleotide phosphate (NADPH) required for fueling antioxidant machinery and producing biosynthetic precursors required for repairing DNA damage (Hurbain et al., 2022; Lamonte et al., 2013). A significant increase in metabolic flux in this pathway is commonly observed in any living cells subjected to oxidative stress. The NADPH generation is important for the GSH pathway in adult brain and spinal cord, which can contribute to detoxify ROS (Bonvento & Bolaños, 2021). Moreover, in post-mitotic cells such as neurons, most PPP-derived NADPH is mainly used as a cofactor for the regenerating pathway of antioxidant GSH, which is reduced from its oxidized form (glutathione disulfide; GSSG) through a reaction catalyzed by glutathione reductase (Bolaños et al., 2008; Kletzien et al., 1994). In fact, the antioxidant role of the PPP has been demonstrated in neurons and in astrocytes (Ben-Yoseph et al., 1996; Kussmaul et al., 1999), in which H_2O_2 causes considerable stimulation of PPP activity eliciting cell protection against H_2O_2 toxicity (Bolaños et al., 2008).

Both antioxidant defense and redox homeostasis are affected by ROS. The excessive ROS formation during reoxygenation leads

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to necrotic and apoptotic cellular death and can contribute to the development of neurodegeneration (Nalivaeva & Turner, 2017). As the antioxidant defense effectiveness depends on the level of NADPH, any alterations of the PPP enzyme activity can influence ROS-induced cellular death (Vetrovoy et al., 2019).

5 | TREATMENT OF SCI BASED ON DRUGS WITH ANTIOXIDATIVE EFFECTS

SCI disrupts the dynamic balance of redox reactions among normal physiological processes, leading to mitochondrial dysfunction and excess ROS production; these changes cause cellular metabolic disorders and functional abnormalities, damage to DNA and proteins, and the induction of apoptosis, all of which exacerbate SCI. Therefore, inhibition of oxidative stress and apoptosis after SCI can protect neurons and minimize SCI. Strategies to manage oxidative stress in SCI include blocking the source of ROS production or promoting the clearance of excess ROS, as well as interfering with the gene expression/protein function of pro-oxidant or antioxidant enzymes (Table. 1).

5.1 | Superoxide dismutase

One of the most important endogenous antioxidants is the enzyme SOD which rapidly catalyzes the dismutation of $O_2^{\cdot-}$ into H_2O_2 and oxygen to regulate the balance of intracellular ROS. The generated H_2O_2 is further converted to oxygen and water by catalase (Hall et al., 2019; Ji et al., 2022). SOD is a mitochondrial antioxidant that catalyzes the dismutation of superoxide produced during mitochondrial respiration; it can also neutralize ROS. Wu et al. (Jiang et al., 2016) reported that ROS, H_2O_2, and MDA levels increased after SCI, while SOD activity and GSH levels decreased; this downregulated antioxidant capacity was reversed by cumene treatment. In addition, in rabbits with acute SCI, SOD levels increased by 33% and MDA levels decreased by 50% after subarachnoid injection of *Salvia divinorum* (Yu et al., 2019). Many studies have also shown that overexpression of SOD1 in cells or animals can attenuate and control neuronal injury (Dimayuga et al., 2007). Moreover, it has been shown that reduced lifespan and extensive oxidative damage were attained via *SOD1* knockout in mice (Elchuri et al., 2005). Therefore, exploring novel drugs targeting SOD to improve SCI and functional recovery by effectively extenuating the inflammation and generation of ROS is essential. For example, Li et al. developed a highly bioactive iridium complex (IrFPHtz) with enhanced antioxidative activities and improved SCI therapeutic efficacy (Ji et al., 2022). Mechanically, IrFPHtz directly targets SOD1 and upregulates the expression of SOD1 to eliminate the excess ROS production induced by SCI, and thus protecting neuron cells from further damage. Moreover, Andrabi et al. developed a nanoparticle loaded SOD protected injured spinal cord from neuronal cell apoptosis by attenuating mitochondrial dysfunction after SCI (Andrabi et al., 2020). Recently, efforts have been made to synthesize mimetics with SOD-like activity, but these experiments have not progressed beyond the preclinical stage. Other studies have shown that phosphocreatine can block ROS and SOD efflux, facilitate oxidative phosphorylation to reduce intracellular ROS levels, and significantly enhance the activities of respiratory chain enzymes to maintain the normal intracellular redox state (Li et al., 2018).

5.2 | Iron chelator

Iron is the most common catalyst involved in free radical generation and oxidative stress. In SCI, the pH of damaged tissue dramatically decreases, which releases large amounts of iron ions that can generate ROS through the Fenton reaction. Iron chelators can inhibit the iron-catalyzed Fenton reaction by chelating free iron, which is a promising strategy to counteract oxidative stress after SCI. An important class of phytochelators comprises metal chelating site polyphenols with high affinity for iron (e.g., caffeic acid, gallic acid, protocatechuic acid, and catechins); these chelators function as antioxidants through inhibition of the iron-catalyzed Fenton reaction (Kontoghiorghes & Kontoghiorghe, 2020). Desferrioxamine, a drug with an iron-chelating site, can cross the blood–brain barrier to reach high therapeutic concentrations in brain tissue (Hua et al., 2008); this drug modulates the expression of genes regulating iron metabolism, the activity of binding proteins, and the expression of genes for antioxidant enzymes that inhibit apoptosis through interactions with chelated trivalent iron and iron-containing heme. However, natural chelators (e.g., phytochelators) and drugs with chelating sites can interfere with iron absorption in the gastrointestinal tract.

5.3 | NOX inhibitors

The NADPH oxidase (NOX) family is characterized for being membrane proteins that use NADPH as an electron donor. The first enzyme belonging to this family of oxidases was identified in 1986. It was located in the membrane of phagocytic cells, and it was found to be a protein capable of generating H_2O_2 using NADPH as a substrate. This enzyme was named NOX2/gp91PHOX (García et al., 2023). Since then, six more isoforms have been identified, constituting the family of NADPH oxidases, whose seven members are called NOX 1–5 and dual oxidases DUOX 1–2 (Bedard & Krause, 2007; Buvelot et al., 2019). NOX is the only oxidase that produces ROS; inhibition of NOX has shown promise as a therapeutic option in preclinical SCI studies. NOX2 inhibition has been shown to reduce oxidative stress and improve functional recovery after SCI (Sabirzhanov et al., 2019; Smith et al., 2022). Using the nonspecific NOX inhibitor apocynin, Zhang, Bailey, et al. (2019) indicated that acute systemic NOX inhibition improved functional recovery in aged, but not young, female mice, suggesting an age-related impact of treatment. These functional improvements were associated with significant reductions in macrophage invasion and macrophage-related ROS production. Moreover, the potential applications of inhibiting NOX1, NOX2, and NOX4 have been demonstrated in nonhuman animal models using genetic deletions (Teixeira et al., 2017). Two types of reagents are available to inhibit NOX: some inhibit enzyme activity and others

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TABLE 1 SCI treatment based on antioxidative stress drugs.

Approach		Mechanism of antioxidative effect	Effect	References
Medicinal treatment	SOD2	Dismutation of superoxide	Neutralization of ROS and reduction of ROS generation	Jiang et al. (2016); Li et al. (2018); Yu et al. (2019)
	Iron chelator	Chelation of iron	Inhibition of Fenton reaction, reduction of iron deposition and ROS release, and promotion of antioxidant enzyme gene expression	Hua et al. (2008); Kontoghiorghes and Kontoghiorghe (2020)
	Minocycline	Inhibition of iron-induced lipid peroxidation	Reduction of malondialdehyde level; inhibition of the activation of IL-1β, tumor necrosis factor-α, cyclooxygenase-2, and matrix metalloproteinases; and elevation of SOD and GSH activities	Aras et al. (2015); Chen-Roetling et al. (2009); Kraus et al. (2005); Pourkhodadad et al. (2019); Shultz and Zhong (2017); Sonmez et al. (2013); Zhang, Xiang, et al. (2019)
	Sulfide	Signaling molecule	Reduction of NO, MDA, and advanced oxidative protein product levels	Kumbasar et al. (2018); Yang et al. (2017)
	PPAR-γ	Inhibition of ROS generation/ maintenance of inflammatory balance	Reduction of proinflammatory factor expression, ROS levels, and neuronal damage; activation of the Nrf2 signaling pathway	Cao et al. (2018); Girnun et al. (2002); Meng et al. (2018); Park et al. (2007)
Targeted therapy	NOX inhibitor	Inhibition of enzyme activity/assembly of enzymes	Inhibition of ROS production	Cifuentes-Pagano et al. (2015); Lv et al. (2015); Nadeem et al. (2021); Teixeira et al. (2017)
	Nrf2	Initiation of antioxidant enzyme expression	Increased expression of antioxidant enzymes, such as SOD, HO-1, and GSH	Lin et al. (2019); Ma (2013); Robledinos-Antón et al. (2019); Schottlender et al. (2021); Sng et al. (2022); Wu et al. (2022); Xia et al. (2017)
	HO-1	Rate-limiting enzyme for heme catabolism and iron production	Reduction of ROS accumulation and apoptosis rate	Bi et al. (2020); Chen-Roetling and Regan (2017); Robinson et al. (2009)

block assembly of the NOX2 enzyme. Among reagents that inhibit enzyme activity, allicin is commonly used as an antioxidant in research studies; its protective effect depends on enhancements of HSP70 protein expression and NADH levels to counteract ROS via NOX downregulation (Nadeem et al., 2021). No effect of allicin was observed in Nrf2 knockout animals, suggesting that the effect of allicin also involves the Nrf2-ARE pathway (Lv et al., 2015). Compared with enzyme activity inhibitors, small peptides that inhibit NOX complex assembly exhibit greater specificity for NOX subtypes, but none of these small peptides have entered clinical trials (Cifuentes-Pagano et al., 2015).

5.4 | Minocycline

Minocycline hydrochloride (MH), a semi-synthetic tetracycline derivative, is a clinically available antibiotic and anti-inflammatory drug that also exhibits potent neuroprotective activities. It can potentially target a broad range of secondary injury mechanisms, and protect neural tissue from multiple neurotoxic insults after SCI, via its anti-inflammatory, antioxidant, and antiapoptotic properties (Shultz & Zhong, 2017). MH directly scavenges free radicals, reduces degradation of deoxyribose by Fe^{2+}/ascorbic acid/hydrogen peroxide, and inhibits iron-induced lipid peroxidation (Kraus et al., 2005). MH penetrates the blood–brain barrier and can significantly inhibit lipid peroxidation after SCI, leading to a decrease in the level of MDA (a byproduct of lipid peroxidation); thus, MH exhibits antioxidative properties (Chen-Roetling et al., 2009; Sonmez et al., 2013). MH treatment after SCI significantly inhibits the activation of IL-1β, tumor necrosis factor-α, cyclooxygenase-2, and matrix metalloproteinases after SCI; it also leads to increases in the activities of SOD and GSH, which are responsible for free radical neutralization (Aras et al., 2015; Zhang, Xiang, et al., 2019). Olfactory sheath cell transplantation 1 week after SCI can affect oxidative stress and proinflammatory factors; combined treatment with MH revealed significant antioxidant effects (Pourkhodadad et al., 2019). The mechanism underlying the protective effect of olfactory sheath cell transplantation is not fully understood and further studies are needed. The findings outlined above suggest that the powerful antioxidant

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mechanism of MH to reduce secondary damage after SCI may be achieved by reducing free radical production and promoting the direct scavenging of free radicals (Shultz & Zhong, 2017).

5.5 | Sulfides

Hydrogen sulfide (H_2S) is a colorless, toxic gas with the odor of rotten eggs; it is a transmitter involved in the regulation of multiple signaling pathways. After intraperitoneal injection of NaHS in a rat SCI model, Yang et al. (2017) reported significant increases in bone density in the femur and tibia, as well as decreases in osteoclast numbers and the extent of surface erosion. MDA levels in the serum and femur of SCI rats in the exogenous H_2S treatment group were also reduced, suggesting that exogenous H_2S treatment could attenuate the oxidative stress caused by SCI. In rabbits with ischemic SCI, α-lipoic acid administration before aortic blockade was able to reduce plasma and spinal cord levels of $NO^{\cdot-}$, GSH, MDA, and late oxidized protein products; it had a significant neuroprotective effect (Kumbasar et al., 2018).

5.6 | Peroxisome proliferator-activated receptor gamma agonist

Peroxisome proliferator-activated receptor gamma (PPAR-γ), a member of the PPAR family, protects cells from oxidative damage and maintains inflammatory homeostasis by inhibiting ROS production and regulating NF-κB pathway signaling molecules (Cao et al., 2018). Xia et al. found that the PPAR-γ agonist pioglitazone inhibited the activity of Rac1, the production of ROS, and the apoptosis induced by ischemia/hypoxia in both the middle cerebral artery occlusion (MCAO) and in vitro oxygen–glucose deprivation (OGD) models, indicating that PPAR-γ inhibits the activation of Rac1/ROS signaling (Xia et al., 2018). Moreover, PPAR-γ also accelerates the removal of excess superoxide molecules by increasing the production of antioxidant enzymes (Ding et al., 2020). The CAT and SOD gene promoters contain peroxisome proliferator response element (PPRE), indicating that they are directly regulated by PPAR-γ (Ding et al., 2020; Hwang et al., 2005). Moreover, PPAR-γ directly regulates the promoters of genes that encode the antioxidant enzymes catalase and SOD, which are upregulated after SCI (Girnun et al., 2002; Park et al., 2007). Rosiglitazone, a synthetic PPAR-γ agonist, indirectly inhibits NF-κB by activating the transcription factor Nrf2, which reduces the production of ROS that are required to activate NF-κB (Meng et al., 2018). In addition, pioglitazone can significantly enhance the induction of neuroprotective heat shock proteins and antioxidant enzymes; it thus exerts protective effects after SCI (Park et al., 2007).

5.7 | Nuclear factor erythroid 2-related factor 2

The main antioxidant capacity of normal physiological function arises from the endogenous antioxidant defense system; enhancement of this defense system by exogenous drugs may be effective for management of oxidative stress. During activation of the Keap1-Nrf2-ARE pathway after SCI, Nrf2 is separated from Keap1 and translocates into the nucleus, where it binds to AREs of target genes that encode various downstream antioxidant enzymes (e.g., SOD, glutathione peroxidase-1, heme oxygenase-1, glutathione transferase, and NAD(P)H quinone oxidoreductase-1) and induces the expression of those genes (Wu et al., 2022). Hyperbaric oxygen therapy induces transcription factor activation and gene expression through the Nrf2 pathway, thus eliciting antioxidant enzyme activity (Schottlender et al., 2021). Dietary Nrf2 activators, including curcumin, carotenoid, and resveratrol, have been developed as daily supplements; some Nrf2 activators are in clinical trials for disease treatment (Robledinos-Antón et al., 2019). Activated T-cell nuclear factor 5 can stimulate the Sirtuin1/Nrf2 pathway in astrocytes to obtain protective effects against oxidative stress (Xia et al., 2017). Ginsenosides modulate the Bax/Bcl2 ratio and stimulate the production of SOD, glutathione peroxidase, and catalase; these activities improve the level of antioxidant stress after SCI through activation of the Nrf2/HO-1 pathway (Sng et al., 2022). 2-(-2-Benzofuranyl)-2-imidazoline protects neurons by activating the Nrf2/HO-1 pathway to increase antioxidant activity; it inhibits neuronal apoptosis by modulating antioxidant damage and directly blocking apoptosis (Lin et al., 2019). The absence of Nrf2 signaling inhibits the induction of target antioxidant enzymes in response to oxidative stress; it also increases susceptibility to oxidative damage (Ma, 2013). Recently, Guo et al. performed a review discussed the roles of Nrf2 in SCI and provided Nrf2-targeted strategies for the treatment of SCI (Guo et al., 2022). Therefore, exogenous activation of the Nrf2 signaling pathway represents a promising protective countermeasure for treating and delaying secondary damage from SCI.

5.8 | Heme oxygenase

Heme oxygenase reduces overall ROS production by scavenging the potentially toxic pro-oxidant heme; it also produces the metabolites biliverdin/bilirubin and carbon monoxide (CO), which have antioxidant properties and can release free iron. Heme oxygenase-1 is a core enzyme in the catalytic metabolism of heme and iron, although it is present at only low levels in neurons (Robinson et al., 2009). In a rat SCI model, intrathecal injection of an HO-1-carrying nucleus-specific adenoviral vector into the 10th thoracic vertebra limited the ER stress-related protein misfolding oxidative impairment and reduced the unfolded protein response; this alleviated ER stress-related ROS production and restored function to the damaged spinal cord (Bi et al., 2020). Heme oxygenase-2 is predominantly expressed in neurons; knockdown of this protein led to significantly less heme or hemoglobin-induced ROS production and cellular damage (Chen-Roetling & Regan, 2017). An important feature of HO-1 regulation is the capacity for extensive and rapid induction of protein levels. This occurs not only in response to elevated levels of heme or hemoproteins, such as hemoglobin, but also in response to a large number

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of endogenous chemicals and xenobiotics (Syapin, 2008). Although there are many different stimuli for the induction of HO-1, a common feature for many is their electrophilic chemistry and the generation of reactive oxygen and/or nitrogen species, which causes the activation of the transcription factor Nrf2 (Kensler et al., 2007). Therefore, the Nrf2/HO-1 signaling pathway is an important cell signal transduction pathway, which plays a key role in the oxidative stress response after SCI.

6 | INTERCONNECTION OF INFLAMMATORY RESPONSE, APOPTOSIS, AUTOPHAGY, AND OXIDATIVE STRESS

The pathological changes in SCI are extremely complex; the secondary injury phase of SCI is characterized by a cascade of oxidative stress-inflammatory responses, microglia activation, apoptosis, and autophagy (Filippone et al., 2020). Thus, an oxidative-inflammatory cascade reaction persists, which can induce autophagy and irreversible apoptosis in neuronal cells (Figure 4).

SCI is a condition primarily characterized by a widespread inflammatory response. There is currently considerable research interest regarding the relationship between oxidative stress and inflammatory responses. ROS have been shown to elicit proinflammatory mediators (e.g., tumor necrosis factor-α, IL-6, and monocyte chemotactic protein-1), mainly through stimulation of the NF-κB signaling pathway and subsequent activation of stress-sensitive kinases, such as c-Jun N-terminal kinase, protein kinase C isoforms, p38-MAPK, and the inhibitor IκB kinase-β (Ham et al., 2013; Rahman et al., 2002; Salzano et al., 2014). These inflammatory mediators activate the NF-κB signaling pathway, resulting in increased expression levels of proinflammatory cytokines such as IL-6 and IL-8; this induces further ROS production. The resulting positive extracellular feedback loop amplifies inflammation and exacerbates nerve damage after SCI (Wiegman et al., 2015). In addition, oxidative stress can promote cellular senescence, especially in adipocytes (Lafontan, 2014; MacKellar et al., 2010), presumably in relation to lipid peroxidation. Adipocyte senescence recruits macrophages and enhances the production of proinflammatory cytokines (Li et al., 2020; Qu et al., 2016). Macrophage activation and the presence of ER stress may lead to simultaneous production of ROS and proinflammatory cytokines (Gratas-Delamarche et al., 2014). Oxidative damage and inflammatory responses to crosstalk thus have important roles in amplifying the effects of SCI.

The antioxidant response and autophagy are simultaneously induced by oxidative stress conditions; these processes decrease ROS and RNS concentrations, while reducing oxidative damage to biomolecules and organelles. ROS act as signaling molecules for the autophagic machinery through targeting effects on autophagy genes (e.g., ATG4), transcription factors (e.g., hypoxia-inducible factor-1α), and signaling pathways (e.g., mechanistic target of rapamycin and MAPKs). These molecules signal to the autophagic machinery and induce autophagy through negative feedback loops; they attempt to restore systemic oxidative homeostasis, while eliminating oxidative damage (Turtle et al., 2019). Additionally, the generated ROS can activate hypoxia-inducible factor-1α transcription factor, p53, FOXO3, and Nrf2, which then induce the expression of autophagy-related factor p62, resulting in the degradation of Keap1 and release of Nrf2;

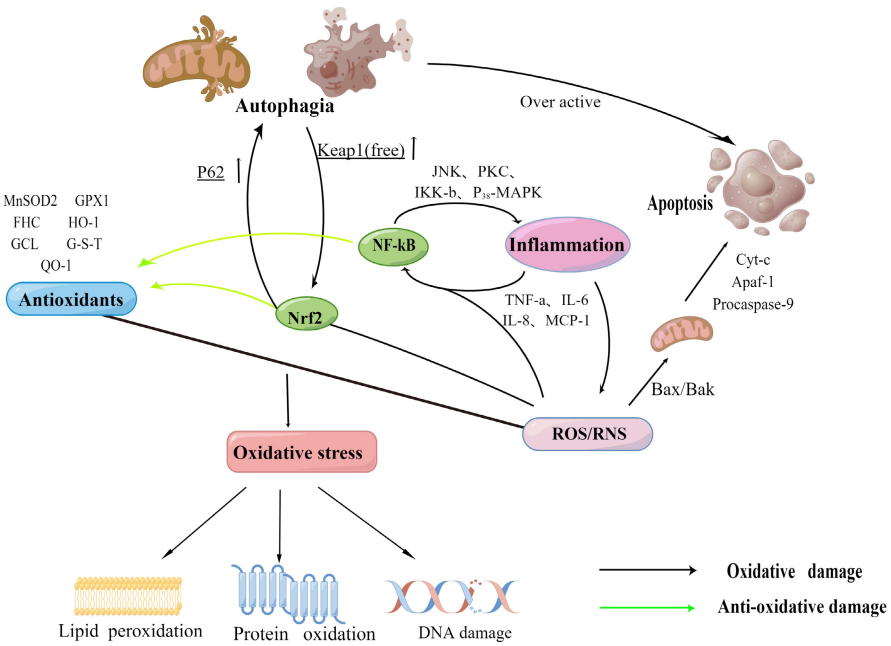


FIGURE 4 Crosstalk among the inflammatory response, apoptosis, autophagy, and oxidative stress. After oxidative stress injury, ROS induce the oxidative-inflammatory cascade response and autophagy mainly by stimulating NF-κB and the Nrf2 signaling pathway; this elicits positive intra- and extracellular feedback loops. In addition, upregulation of the proapoptotic proteins Bax and Bak leads to the release of proapoptotic factors from mitochondria; these factors induce neuronal apoptosis and exacerbate nerve injury after SCI.

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this forms a positive feedback loop (Lau et al., 2010; Scherz-Shouval & Elazar, 2011). In experimental studies, exogenous H_2O_2 activated both autophagy and apoptosis in mammalian cells; the affected cells exhibited low Bcl2 levels and high Bax levels, loss of mitochondrial membrane potential, and release of cytochrome c. H_2O_2 induces autophagy and stimulates apoptosis by increasing Beclin-1 expression and decreasing mechanistic target of rapamycin activity (Tan et al., 2018; Zhao et al., 2020). Oxidative stress causes DNA damage, which induces both cell cycle arrest and autophagy (Dotiwala et al., 2013). Appropriate upregulation of autophagy promotes the breakdown of damaged proteins and inhibition of apoptosis (Casili et al., 2020). However, excessive activation of autophagy leads to autophagic cell death (Zhou et al., 2017).

Excessive ROS production induces apoptosis-related cellular activities; the apoptotic pathway is mediated by altered protein levels of Bcl2 family members. The proapoptotic Bax/Bak inserts itself into the mitochondrial membrane after oligomerization in the outer mitochondrial membrane (Hollville et al., 2019), leading to permeabilization of the outer mitochondrial membrane and release of proapoptotic factors into the cytoplasm; these factors include cytochrome c, Smac/DIABLO, EndoG (a nuclease), apoptosis-inducing factor (an oxidoreductase), and HtrA2/Omi (a protease). In the presence of ATP, cytochrome c, apoptotic protease activating factor 1, and procaspase-9 oligomerize to form apoptotic vesicles. Procaspase-9 forms homodimers that initiate the production of active Caspase-3/7/9 and promotion of apoptosis in neuronal cells (Roberts et al., 2022). Mitochondrial permeabilization and cytochrome c release after apoptotic stimuli are considered cellular points of no return, from which cells do not recover. Healthy neurons are extremely glycolytic; released cytochrome c is kept in a reduced (possibly inactive) state, from which it cannot activate caspases. Increased ROS levels create a more oxidative cellular environment, increasing neuronal susceptibility to cytochrome c-mediated caspase activation and promoting the apoptotic process (Ramzan et al., 2020; Schieber & Chandel, 2014; Vaughn & Deshmukh, 2008). Moreover, the accumulation of ROS and other factors (e.g., iNOS) leads to neuronal and glial cell apoptosis within the first 24 h after SCI (Filomeni et al., 2015).

7 | SUMMARY AND OUTLOOK

The pathophysiological processes that occur after SCI are complex; imbalance between pro-oxidants and antioxidant systems leads to excessive ROS production. High levels of ROS can cause irreversible oxidative damage to macromolecules, (e.g., nucleic acids, lipids, and proteins) and interactions with inflammatory responses, cellular autophagy, and apoptosis; these processes can lead to a complex cascade of secondary damage. This complexity may explain why many treatment strategies and experimental methods have not been successful in SCI treatment. Oxidative stress has an important role in secondary damage after SCI; the levels of various free radicals can serve as indicators of damage. ROS levels can be regulated through the Nrf2 signaling pathway; this regulation can help to prevent or reduce secondary damage after SCI. A clearer understanding of the mechanisms by which ROS directly regulate relevant signaling pathways will provide clarity concerning the mechanisms that underlie the onset and progression of oxidative stress after SCI; this understanding will also aid in the identification of new therapeutic targets. Research thus far has highlighted the need for improvements in existing drugs and the identification of new drugs for more effective antioxidant therapy in SCI. Further studies are needed before these new treatment strategies can be applied in clinical practice.

AUTHOR CONTRIBUTIONS

Mengsi Yu, Zhiying Wang, Yonggang Wang: study design, review and editing. Zhanjun Ma: writing, review and editing, critical revision of the manuscript. Other authors: review and editing. All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no competing interests.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are openly available in PubMed at https://pubmed.ncbi.nlm.nih.gov/. Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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