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REVIEW ARTICLE

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Biochemical and cellular basis of oxidative stress: Implications for disease onset

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Abstract

Cellular oxidation–reduction (redox) systems, which encompass pro- and antioxidant molecules, are integral components of a plethora of essential cellular processes. Any dysregulation of these systems can cause molecular imbalances between the pro- and antioxidant moieties, leading to a state of oxidative stress. Long-lasting oxidative stress can manifest clinically as a variety of chronic illnesses including cancers, neurodegenerative disorders, cardiovascular disease, and metabolic diseases like diabetes. As such, this review investigates the impact of oxidative stress on the human body with emphasis on the underlying oxidants, mechanisms, and pathways. It also discusses the available antioxidant defense mechanisms. The cellular monitoring and regulatory systems that ensure a balanced oxidative cellular environment are detailed. We critically discuss the notion of oxidants as a double-edged sword, being signaling messengers at low physiological concentrations but causative agents of oxidative stress when overproduced. In this regard, the review also presents strategies employed by oxidants including redox signaling and activation of transcriptional programs such as those mediated by the Nrf2/Keap1 and NFk signaling. Likewise, redox molecular switches of peroxiredoxin and DJ-1 and the proteins they regulate are presented. The review concludes that a thorough comprehension of cellular redox systems is essential to develop the evolving field of redox medicine.

KEYWORDS

antioxidants, NFκB, NOX, Nrf2, peroxiredoxin, ROS

1 | INTRODUCTION

Oxidation and reduction systems, comprising pro- and antioxidant molecules, respectively exist in cells. These two systems constitute what is called the cellular oxidation–reduction (redox) system, an integral component of numerous cellular processes. Under physiological conditions, a delicate and dynamic balance exists within the redox systems, and that culminates in the cellular redox state. It is well established that disruption of this balance results in a state of oxidative stress that can damage molecular components such as

Karl Aramouni and Roland Assaf contributed equally to this study.

DNA, lipids, and proteins (Figure 1) and contributes to the onset and progression of pathological states (Al Attar et al., 2022; Badran et al., 2020; Bhagani et al., 2020; Mesmar et al., 2021; Shaito et al., 2022; Slika et al., 2022). As a result, cells expend energy to maintain a balanced redox state through mechanisms that ensure "redox homeostasis." Due to the complexity of living systems, no absolute redox state exists in an organism, not even in a single cell, and redox setpoints can vary from one cellular compartment to another, depending on physiological conditions (Ma, 2013; Sies et al., 2017). Redox systems involve two classes of molecules: prooxidants and antioxidants. These can vary in concentration depending on their cellular location, levels of gene expression of the proteins involved in redox reactions, mitochondrial metabolism, as well as on exogenous factors such as ambient molecular oxygen (O_2) levels (Sies et al., 2017). Nonetheless, there exists a well-controlled, optimal, and delicate balance between antioxidants and prooxidants under specific physiological conditions (Culp et al., 1979). As such, it is critical to balance such physiological redox states, otherwise tilting the balance toward either prooxidants or antioxidants can contribute to the development of pathological states including cancers such as breast and prostate cancers (Jorgenson et al., 2013), and chronic diseases such as Alzheimer's and Parkinson's disease (Ma, 2013; Pizzino et al., 2017).

Oxidative stressors are varied and have been classified according to their form, intensity, or biological responses. Oxidants are mainly assigned to two groups: free radicals, which have a free electron such as the superoxide anion radical ($O_2^{-\bullet}$) and nonradicals which are chemically stable molecules such as hydrogen peroxide (H_2O_2) (Sies et al., 2017). Oxygen reactive species (ROS) are the most renowned oxidants, but reactive nitrogen, chlorine, bromide, sulfur, carbonyl, or even selenium species have been shown to exist at the cellular level and to share in redox homeostasis (DeLeon et al., 2016; Giles et al., 2001; Poole, 2015).

The present review investigates the impact of oxidative stress on the human body with emphasis on the underlying mechanisms and pathways. The different types of prooxidants as well as the available cellular antioxidant systems are discussed. The strategies inherent to antioxidant action that counteract oxidative stress are detailed. The notion of oxidants as a double-edged sword, by acting as signaling messengers at low physiological concentrations or causative agents of oxidative stress when overproduced, is also discussed. Specifically, the review focuses on strategies employed by oxidants including redox signaling and activation of transcriptional programs such as those mediated by the Nrf2/Keap1 signaling.

2 | OXIDATIVE DAMAGE OF CELLULAR COMPONENTS

Normal metabolic processes can generate an excess of various oxidant molecules, leading an oxidative state which is usually balanced by reduction scavenging systems. Yet, when this oxidative state fluctuates substantially beyond the optimal limit, oxidative

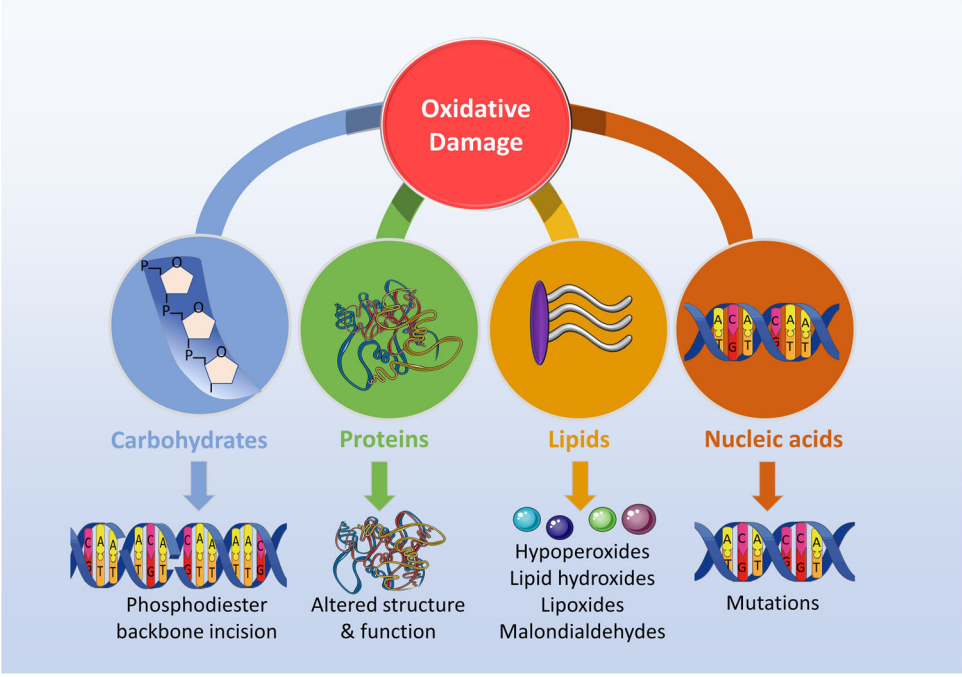

FIGURE 1 Oxidative stress leads to damage of various macromolecules. In oxidative milieu, reactive oxygen species, along with other oxidative molecules, impact significantly deleterious effects on biomolecules. Among the damages are changes in the carbohydrate moieties that could precipitate phosphodiester backbone incision in DNA. Other damages induce conformation changes in proteins, followed by functional aberrations. Likewise, lipids could be oxidized to various potentially toxic molecules like lipoxides. Perhaps one of the longer-lasting effects of oxidative damage is mutations that could occur in the genome.

distress ensues. This state of excessive oxidation can lead to oxidative damage involving a diverse range of biomolecules, including nucleic acids, proteins, lipids, and carbohydrates (Figure 1).

At the level of nucleic acids, both DNA and RNA are deleteriously impacted by oxidative milieu. Indeed, spontaneous DNA mutations, which precipitate genome instability, take place more often under oxidative stress (Storz et al., 1987). Particularly, guanine is the most susceptible DNA base; it is modified into 8-oxo-7,8-dihydroguanine, which can base-pair with adenine resulting in transverse mutations once DNA replication is completed (Freudenthal et al., 2015). Moreover, RNA is also subject to oxidative damage, where 8-Oxoguanine in RNA compromises translational fidelity, thus contributing to various diseases (Chen et al., 2022; Hahm et al., 2022; Poulsen et al., 2012).

Reaction of oxidation products to amino acid side chains can determine the overall structure and function of proteins (Davies, 2016; Griffiths et al., 2014; Kim et al., 2015). The endoplasmic reticulum (ER) is the site of oxidative protein folding which occurs via the formation of disulfide bonds usually between cysteine residues of proteins (Oka & Bulleid, 2013). Many enzymes are involved in this process and include the protein disulfide isomerase family of dithiol-disulfide oxidoreductases, peroxiredoxin IV, glutathione-dependent peroxidase 7 and 8 (GPx7 and GPx8), and the pathways of ER oxidoreductin 1 (Ero1). After the formation of disulfide bonds by Ero1, a molecule of H_2O_2 is produced and gets trapped in the ER by the activity of GPx8 (Ramming et al., 2014). Likewise, GPx7 acts as a novel oxidative stress sensor and regulates thio-containing proteins to maintain physiological redox homeostasis (Kanemura et al., 2020). Following an increase in ER stress and accumulation of unfolded proteins, the unfolded protein response (UPR) pathway is activated. In UPR, integration of other redox signals with the activity of chaperones will re-establish a state of redox homeostasis. Importantly, when UPR fails to achieve redox homeostasis, cell death becomes eventual (Hartl et al., 2011).

Lipids can also be oxidized under oxidative stressful conditions, and the oxidized lipids thus formed can act as ligands for the peroxisome proliferator-activated receptor (Davies et al., 2001). These products include lipid hydroperoxides, hydroxides, epoxides, malondialdehydes, and several more (Niki, 2014; Spickett & Pitt, 2015).

Similarly, carbohydrates are also subject to oxidation reactions, which can disrupt their structure and function. For instance, modification of the sugar backbone in DNA can result in DNA strand breaks. Oxidation products of free carbohydrates include reactive carbonyls (Robertson, 2004). Likewise, nonenzymatic glycosylation, glycation, and GlcNAcylation can all increase under oxidative stress (Sies et al., 2017).

3 | ANTIOXIDANT SYSTEMS INSIDE THE CELL: CELLULAR DEFENSE AGAINST OXIDATIVE STRESS

Due to the cellular damage caused by excessive generation of oxidants, cellular mechanisms for their elimination are of paramount importance and this existence in place becomes rather critical. By virtue of their antioxidant activities, specific enzymes serve as the main artillery against oxidative stress. Superoxide dismutase (SOD), discovered by McCord and Fridovich in 1969, was the first identified prooxidant cellular enzyme system and it catalyzes the dismutation of $O_2^{-\bullet}$ (McCord & Fridovich, 1988). Superoxide anions are mainly produced due to the activity of NADPH oxidases (NOXs), xanthine oxidase, lipooxygenases, and cyclooxygenases, and are dismutated into H_2O_2 by SOD. Catalases constitute another enzymatic antioxidant system and they can dismutate H_2O_2 into O_2 and H_2O. Other enzymatic antioxidant systems in the cell, including a large family of peroxidase enzymes, can also reduce H_2O_2. Peroxidases, most notable of which are the GPx, can reduce H_2O_2 and other hydroperoxides. GPx can reduce H_2O_2 or lipid peroxides by the help of reduced glutathione (GSH). Oxidized glutathione disulfide (GSSG) is produced as a byproduct of GPx reactions, and GSSG is later reduced by glutathione reductase into GSH; thus replenishing GSH and maintaining their high levels inside the cell (Lushchak, 2014). Additional enzymatic antioxidant systems in the cell include glucose-6-phosphate dehydrogenase, 6-phosphogluconate dehydrogenase, NADP-malic enzyme (malate dehydrogenase), and isocitrate dehydrogenase all of which are involved in the conversion of $NADP^+$ into NADPH (Lushchak, 2014).

Collectively, the antioxidant enzymes systems, and other proteins required for redox state regulation, are called high molecular-mass antioxidants. However, the action of these enzyme systems cannot cope with oxidative stress in the organism and other forms of antioxidants, named low-molecular-mass antioxidants, take over in the fight against electronically excited states. Low-molecular-mass antioxidants include compounds whose molecular weight is <1 kDa like vitamins C and E, coenzyme Q10, carotenoids, anthocyanins, GSH, uric acid, and many other small molecules or nutritional compounds both natural or synthetic. They can participate directly in scavenging of free radicals or can serve as essential cofactors for various enzymatic antioxidant systems. They can also directly protect organisms against the hydroxyl free radical (HO•) (Chen et al., 2013; Jones, 2006). As an example of their antioxidative actions, carotenoids can deactivate singlet molecular oxygen and the excited states of carbonyls, resulting from photoexcitation and chemiexcitation (Jones, 2006).

In general, the low molecular-mass antioxidants can act as (1) free-radical terminators, (2) reducing agents or oxygen scavengers, and (3) chelating agents that form stable complexes with prooxidant metal ions (Chen et al., 2013; Dziezak, 1986). The antioxidants modes of action to counteract oxidative stress can be categorized into prevention, interception, or repair (Sies, 1993) (Figure 2).

4 | REGULATION OF REDOX REACTIONS

4.1 | Redox signaling

Redox reactions, including oxidant and redundant molecules, are vital in the regulation of different aspects of a multitude of biological

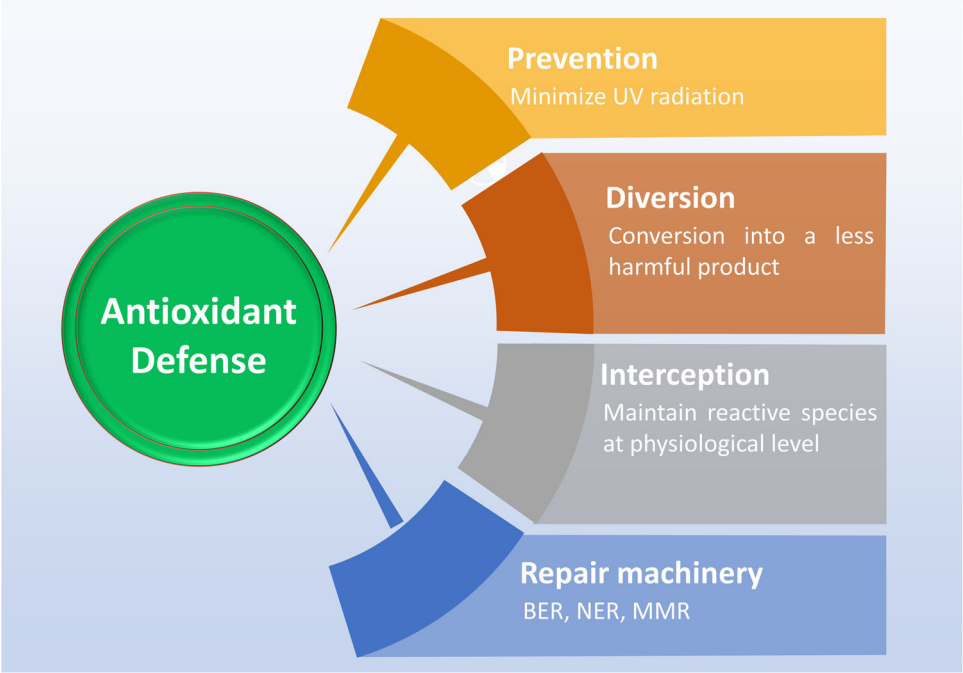

FIGURE 2 Antioxidant defense against oxidative stress. Modes of action of antioxidants to counteract excessive generation of oxidants. Among these are prevention, diversion, interception, and repair mechanisms. BER: base excision repair; NER: nucleotide excision repair; MMR: mismatch repair.

processes. Oxidants are formed under physiological settings at appropriately regulated concentrations that are kept low. Importantly, at these low concentrations, oxidants can act as important signaling molecules in the regulation of vital cellular processes including cell division, inflammation, immune function, autophagy, and stress response (Finkel, 2011). For example, ROS are produced mainly as byproducts of cellular metabolic reactions, where peroxisomes, ER, mitochondrial respiratory chain, and mitochondrial metabolism, xanthine oxidase, lipooxygenases, cyclooxygenase, and NOXs are the major protagonists responsible for ROS generation (Bhardwaj & He, 2020). At physiologically low concentrations, ROS play the role of second messengers in several major signaling pathways that include cell differentiation, growth, and death (Zhang et al., 2016), in addition to being implicated in many physiological processes, such as the regulation of vasotone, immune responses, and several more (Liu et al., 2003). As noted, an imbalance between oxidants and antioxidants leads to exaggerated production of ROS and other reactive species (Alfadda & Sallam, 2012; Finkel, 2011), leading to a state of oxidative stress and then to damage of cellular components (Davies et al., 2001; Finkel, 2011), and eventually disease (Alfadda & Sallam, 2012; Badran et al., 2020; Finkel, 2011; Taniyama & Griendling, 2003).

In context, structure and function of proteins can be altered by reversible and irreversible redox reactions, offering a way of control of protein activation and signaling. This is a frequent means of the regulation of the activities of numerous transcription factors as well as enzymes. For example, the function of the heterodimeric transcription factor activator protein-1 (AP-1), comprised of Fos and Jun proteins, is modulated by the reduction-oxidation state of specific cysteine residues in its DNA-binding domain (Figure 3) (Abate et al., 1990; Liu et al., 2005). Also, reduction of oxidized cysteines within the DNA-binding domain of the transcription factor p53 modifies its DNA binding and transcriptional activity (Liu et al., 2005). Hypoxia-inducible factor 1α is another transcription factor regulated by oxidative stress (Paik et al., 2017). Similarly, enzyme activity is modulated by the redox status; for example, via thiol/disulfide redox changes of specific amino acid residues (Bindoli & Rigobello, 2013; D'Autreaux & Toledano, 2007). Apoptosis Signal-regulating Kinase 1 (ASK1), protein tyrosine kinase, AMP-activated protein kinase, Src kinase, EGF receptor (EGFR), among other enzymes, are classical examples of enzymes regulated by redox status (Heppner et al., 2018; Truong & Carroll, 2013).

As an uncharged molecule, H_2O_2 is well-suited for redox sensing and signaling. It can control protein function and enzyme activity via the oxidative modification of the side chains of cysteine, methionine, proline, histidine, and tryptophan amino acid residues of proteins. H_2O_2 usually reacts sluggishly with biomolecules (reaction rate constant $k_{app} \sim 1 - 10\ M^{-1}s^{-1}$) (Sobotta et al., 2015), but it has the outstanding capability of diffusing away from its generation site, including transport through H_2O_2 aquaporins or peroxiporins, to reach locations where it modulates activity of more reactive target proteins (Bienert et al., 2007; Prata et al., 2019). Nevertheless, the mechanism of how regulatory proteins become oxidized by H_2O_2 remains poorly understood (Winterbourn & Hampton, 2015).

Notably, H_2O_2 was found to interact differently with cysteinyl residues in peroxiredoxins or selenocysteine residues of GPx. Indeed, the presence of H_2O_2 can be sensed by peroxiredoxin-2, which is one

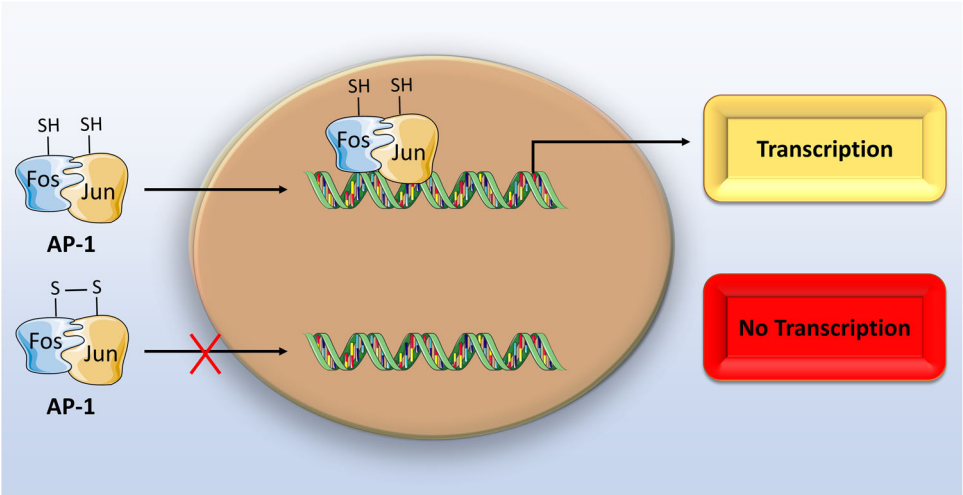

FIGURE 3 Redox regulation of AP-1 transcriptional activity. Under high redox levels, AP-1 forms intra-and intermolecular S–S disulfide bonds between cysteine residues of its Fos and Jun subunits. This crosslinking hinders AP-1 entry into the nucleus and therefore inhibits its transcriptional activity. Even if the S–S crosslinked AP-1 enters the nucleus, it may not be able to bind DNA, since the crosslinked residues are usually located at AP-1 DNA binding domain. AP-1, activator protein-1.

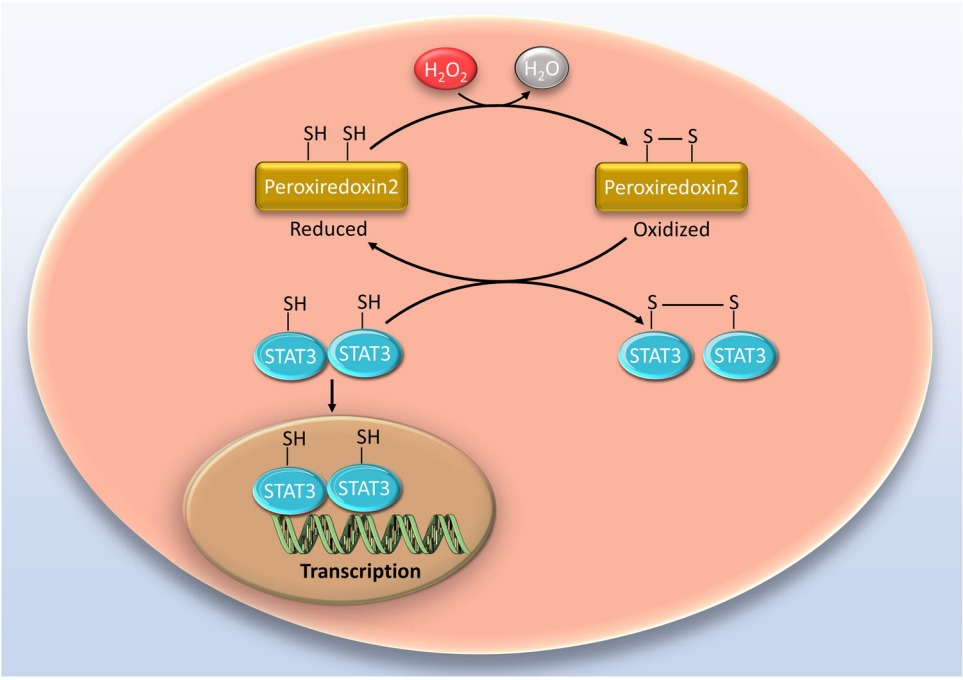

FIGURE 4 Mechanism of activation of a regulatory proteins such as STAT3 by H_2O_2 through peroxiredoxin redox relays. The sensor mechanism for activation of the target, usually regulatory, proteins includes oxidation of a peroxiredoxin sensor to its disulfide form, then the oxidation equivalents are transmitted to the target (STAT3 in this case), oxidized target protein is produced (disulfide STAT3 oligomers) and the peroxiredoxin sensor is regenerated and available to undergo a new cycle of redox relay. The disulfide form of the target protein will have an attenuated activity, in this case, disulfide STAT3 oligomers cannot translocate to the nucleus to perform their transcriptional activation function to induce cytokine production (Sobotta et al., 2015; Winterbourn & Hampton, 2015).

of the most H_2O_2-reactive proteins in the cell ($k_{app} \sim 10^7 - 10^8$ $M^{-1}s^{-1}$). Upon H_2O_2 binding, oxidative equivalents are transmitted from peroxiredoxin-2 to the redox-regulated transcription factor STAT3 leading to the formation of disulfide-linked STAT3 oligomers which have a compromised transcriptional activity (Figure 4). In this case, peroxiredoxin-2 forms a redox relay for H_2O_2 redox signaling. The use of peroxiredoxins as sensors for transmitting redox signals has been demonstrated in several cellular processes (Winterbourn &

Hampton, 2015). Peroxiredoxin antioxidant cycle is allowed to continue by the action of thioredoxin, a small disulfide reductase partner of peroxiredoxin, and thioredoxin reductase which oxidizes NADPH to reduce thioredoxin (Stancill & Corbett, 2021). Hence, H_2O_2 can act as an intracellular second messenger in signal transduction to modulate protein function by inducing the transient oxidation of protein cysteinyl thiols and the formation of disulfide bonds (Sobotta et al., 2015; Winterbourn & Hampton, 2015). Peroxiredoxin-1 acts redox-relay in the activation of ASK1 (Vo et al., 2021). At high H_2O_2 levels peroxiredoxin-1 directly interacts with ASK1 (Vo et al., 2021), and inhibits ASK1-induced apoptosis (Kim et al., 2008; Zhang et al., 2015). Peroxiredoxin-1 has also been reported to directly interact with p53, c-Myc, and nuclear factor kappa B (NF-κB), among others (Ding et al., 2017).

H_2O_2, similar to other ROS, can act as a signaling molecule when produced as a result of the activation of several receptors such as EGFR and PDGFR. However, H_2O_2 signaling via this mechanism also involves redox sensing by cysteine and tyrosine residues of these receptors as well as other enzymes in the signal transduction pathway (Di Marzo et al., 2018; Finkel, 2011).

The human DJ-1 protein, encoded by Parkinson's disease protein 7 gene, existing in oxidized or reduced form, acts as another oxidative switch, and is known to be an oxidative stress sensor (Zhang et al., 2020). DJ-1 is implicated in incidence of oxidative stress-related diseases and immune and inflammatory disorders such as cancer, neurodegenerative disorders, and type 2 diabetes. DJ-1 modifies the activation of immune cells by ROS-dependent and/or ROS-independent mechanisms (Cao et al., 2015; Girotto et al., 2014; Wilson, 2011; Zhang et al., 2020). DJ-1 is implicated in the regulation of transcription and signaling pathways, scavenging of ROS, thereby acting as an antioxidative stress molecule that regulates mitochondrial homeostasis, Nrf2/Keap1 antioxidant gene expression, and oxidative stress-induced apoptosis by stabilizing the thioredoxin 1/ASK1 protein complex, destabilizing ASK1 homodimerization, and sequestering death-associated protein 6 (Daxx), an ASK1 activator, in the nucleus (Ashley et al., 2009; Clements et al., 2006; Im et al., 2010, 2012; Junn et al., 2005, 2009; Mo et al., 2010; Zhang et al., 2020).

Other reactive species such as sulfide reactive species and nitrogen reactive species, such as nitric oxide (NO), can modulate thiol-based redox signaling. NO, similar to ROS and H_2O_2, is reactive species which acts as a prime signaling molecule. As a free radical, NO can react with $O_2^{-\bullet}$ to form peroxynitrite (ONOO−). This molecule can modify tyrosine amino acid residues in proteins into 3-nitrotyrosine via nitration reactions (Figure 5). In addition, ONOO− can also act as a biological oxidant; it can modulate mitochondrial function and can even trigger apoptosis through its oxidation and nitration reactions (Figure 5) (Beckman et al., 1990).

Thereby, H_2O_2 as well as NO and sulfide reactive species are involved in redox signaling and can eventually modify the activity of biological molecules, especially proteins including enzymes and transcription factors.

4.2 | Molecular redox switches act through major transcription factors

In the cell, molecular redox switches act in an orchestrated fashion to keep the oxidative state of the cell in check. These redox switches,

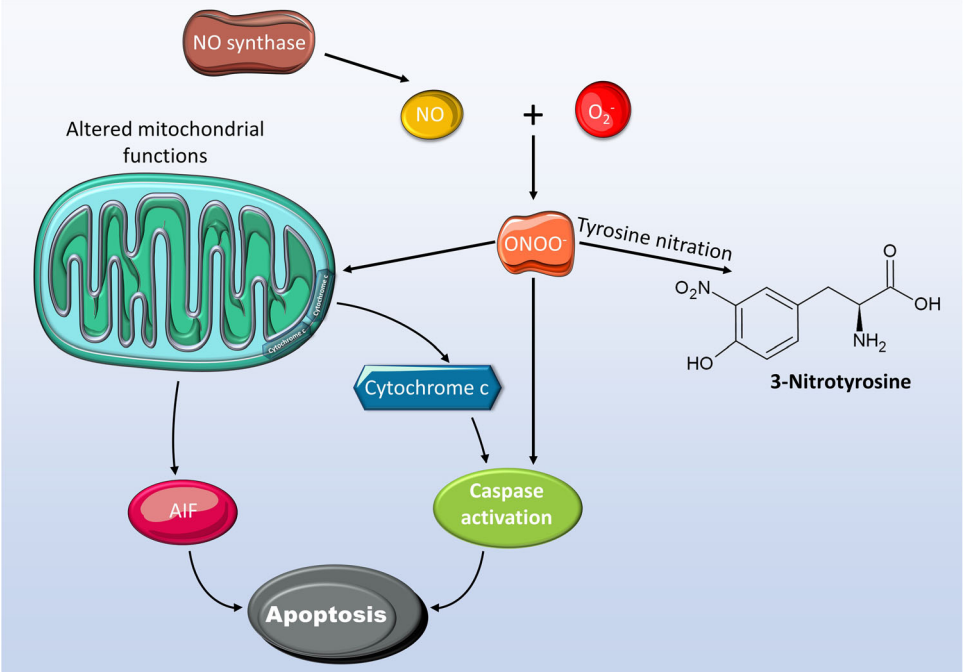

FIGURE 5 Nitrogen reactive species such as ONOO− can modulate cellular process. ONOO− can modify protein function through nitration reactions. Also, ONOO− can modulate mitochondrial function leading to apoptosis.

mostly thiol-based switches, assume such a critical function by virtue of their ability to (1) sense oxidative stress and (2) control redox sensing and signaling. Eukaryotic redox switches participate in the regulation of the transcription factors including nuclear factor-E2-related factor 2/Kelch-like ECH-associated protein-1(Nrf2/Keap1) and NF-κB, which are recognized as prominent master regulators of a broad range of biological functions in mammalian cells.

Nrf2 is a transcription factor that is activated by oxidants and electrophiles to induce the expression of a set of antioxidants and detoxification enzymes with protective properties. Nrf2 target genes include a set of enzymes involved in drug metabolism and deposition such as glutathione S-transferase, NADPH:quinone oxidoreductase 1, and Cytochrome P450 CYP2A5. Nrf2 target genes also include genes encoding for enzymes and proteins involved in antioxidant defense and oxidant signaling such as SOD3, GPx2, and peroxiredoxin-1 and 6 (Ma, 2013). Heme oxygenase 1 (HO-1), which degrades heme and has antioxidant and anti-inflammatory roles, is another interesting transcriptional target of Nrf2 (Araujo et al., 2012). Under unstressed conditions, Nrf2 transcriptional activity is suppressed because of its retention in the cytoplasm by Keap1 (Figure 6). Also, Keap1 promotes ubiquitination of Nrf2 resulting in its degradation by the proteasome (Figure 6) (Antelmann & Helmann, 2011; Itoh et al., 1997; Ma, 2013; Nguyen et al., 2004). However, under stressful conditions, cysteinyl residues of Keap1 are modified to form inter- and intramolecular disulfide bonds and the modified Keap1 can no longer suppress Nrf2. Hence, Nrf2 can accumulate and is free to translocate to the nucleus (Figure 6). In the nucleus, Nrf2 heterodimerizes with small Maf proteins and the heterodimer binds to a DNA sequence called antioxidant response element to induce the expression of its target genes (Antelmann & Helmann, 2011; Ma, 2013; Nguyen et al., 2004). It is estimated that Nrf2 can induce 200 genes, at least, in response to ROS or electrophiles (Antelmann & Helmann, 2011).

As such, Nrf2 is activated during excessive oxidation states and plays an essential role in the induction and regulation of the antioxidant-free radical-scavenging systems that are needed to elevate oxidative stress. Relatedly, any defect in Nrf2 signaling can lead to a premature aging phenotype. In fact, the presence of a mutation in lamin A, encoding for a major architectural protein of the nucleus, can trap Nrf2 at the nuclear periphery, inhibiting its transcriptional activation. Consequently, Nrf2 signaling will be interrupted leading to a state of chronic oxidative stress which later translates into a premature aging phenotype (Kubben et al., 2016). Nrf2 knockout mice are more susceptible to oxidative stress and to a range of chemical toxicant (Kensler et al., 2007; Klaassen & Reisman, 2010; Ma, 2013; Walters et al., 2008). In accordance, increasing Nrf2 activity can protect animal models from damage induced by oxidative stress (Talalay et al., 2003). Likewise, in human patients, Nrf2 mutations have also been reported, and dysregulation of the Nrf2 pathway contributes to carcinogenesis by inducing aggressive cell proliferation (Mitsuishi et al., 2012; Yamaguchi et al., 2019). The mechanisms underpinning the loss of function of Nrf2 in cancer are not yet elucidated. It was proposed that Nrf2 can modify cancer cell metabolism toward the anabolic oxidation of glucose and glutamine, metabolic activities that support cell proliferation in addition to boosting cytoprotective mechanisms (Mitsuishi et al., 2012). Nrf2 genetic variations have been correlated with the incidence of several diseases and their complications (Chen et al., 2019; Korytina et al., 2019; Xu et al., 2016; Yamaguchi

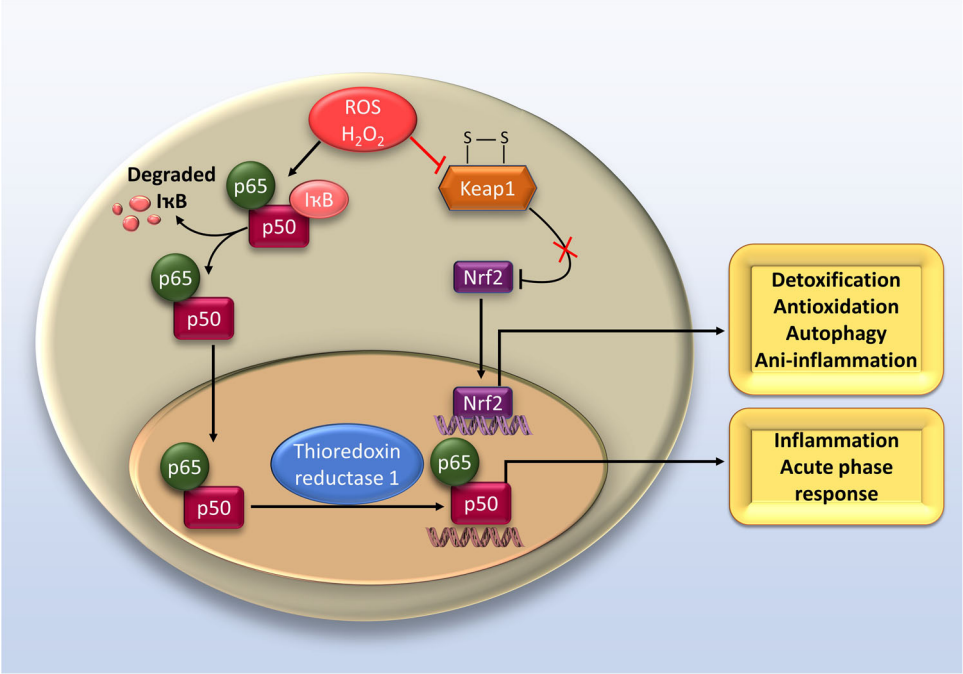

FIGURE 6 Nrf2 can activate defense against oxidative stress through a redox switch that involves Keap1. Nuclear factor kappa B (NF-κB) activation can also involve a redox switch.

et al., 2019; Zazueta et al., 2022). For instance, the presence of certain gene polymorphisms is associated with the development of chronic obstructive pulmonary disease, where a genotype-dependent variation of lung function parameters is noted (Korytina et al., 2019). Similarly, a significant difference in genotypic and allelic frequencies exists between type 2 diabetes mellitus (T2DM) patients with complications versus T2DM patients without complications, although no genetic variation per se appears to underlie the incidence of the disease (Xu et al., 2016). Moreover, patients with renal cell carcinoma respond differently to chemotherapy depending on certain single nucleotide polymorphisms of Nrf2. In this context, it is now documented that tumors with genotypes that tend to increase Nrf2 protein expression are more resistant to treatment, with a consequent reduction in overall survival in these populations (Yamaguchi et al., 2019). These findings reiterate the importance of genetic factors behind chronic diseases, their progression, and the potential role of targeted therapy.

Pharmacological activators of Nrf2, like dimethyl fumarate (available commercially as BG-12 or Tecfidera from Biogen) and Oltipraz (4-methyl-5(pyrazinyl-2)-1-2-dithiole-3-thione), and inhibitors appear to be promising therapeutic tools in the management of several diseases, particularly ones underpinned by oxidative stress and inflammation. For instance, dimethyl fumarate has been FDA approved for relapsing-remitting multiple sclerosis (Xu et al., 2015) and psoriasis (Höxtermann et al., 1998). Recently, it was shown in a multicenter phase II clinical trial that BG-12 can be used in relapsed and refractory cutaneous T-cell lymphoma (Nicolay et al., 2023). Moreover, BG-12 appears to suppress platelet function and thrombus formation (Chu et al., 2023). Several other reports suggest a potential ameliorative role for dimethyl fumarate in Alzheimer's disease, ischemic stroke, systemic lupus erythematosus, traumatic brain injury, among others (Cheng et al., 2023; Mauro et al., 2023; Owjfard et al., 2023). On the other hand, Oltipraz is currently in phase III trial for the treatment of nonalcoholic fatty liver disease (Robledinos-Antón et al., 2019) and is being proposed as potential agent for the management of Thoracic aortic aneurysm and dissection and osteoporosis (Wang et al., 2022; Yang et al., 2022).

Although overwhelming evidence shows its regulatory role as a transcription factor of proinflammatory genes, NF-κB is itself regulated by oxidation species. In the cytoplasm, NF-κB can be modulated by H_2O_2 and other ROS, leading to the dissociation of the inhibitory subunit IκB. NF-κB can then translocate to the nucleus where gene activation is favored under the reductive conditions of the nucleus (Figure 6). This nuclear reductive state is partly attained by the action of the enzyme thioredoxin reductase 1 which can reduce the redox-sensitive cysteine residues in the DNA binding domain of NF-κB, leading to an enhancement of NF-κB DNA binding ability (Figure 6) (Halvey et al., 2007; Heilman et al., 2011; Sakurai et al., 2004). In this regard, NF-κB can be activated by oxidants such as ROS and H_2O_2 to induce the expression of genes involved in inflammatory, immune, and acute phase responses. This allows NF-κB to play a protective role in the early phase of oxidative stress as well as during cell recovery from oxidative stress (Lingappan, 2018).

It should be noted that there is a cell type and tissue-specific interplay between NF-κB and Nrf2 activation. However, the details of this interaction require further elucidation (Wardyn et al., 2015). In general, Nrf2 negatively regulates NF-κB signaling pathways through several mechanisms (Saha et al., 2020). For example, Nrf2 can inhibit degradation of IκB-α and thus prevent the nuclear translocation of NF-κB (Ganesh Yerra et al., 2013; Saha et al., 2020). Along the same lines, Nrf2 can induce expression of HO-1 which can subsequently prevent the degradation of IκB-α (Chen et al., 2018; Saha et al., 2020).

Overall, molecular redox switches keep the oxidative state of the cell in check by sensing oxidative stress and regulation of major transcription factors which can modify the transcriptional profiles of the cell to counteract oxidative stress.

5 | CONCLUSION

Redox equilibrium plays pivotal roles in physiological and pathological processes through numerous receptors, proteins, ions, among other molecules. When the redox equilibrium is imbalanced many signaling pathways are perturbed leading to the onset of various diseases. Unpinning the mechanisms of redox regulation becomes essential for the discovery of new therapies. Plenty of the redox-based signaling mechanisms have been uncovered including redox-switches, prooxidant and antioxidant systems, and the Nrf2/Keap1 and NF-kB signaling. However, these mechanisms are intricate, and our understanding of their complexity is still evolving. Understanding of these mechanisms has led to the development of the field of redox medicine. There are many successful examples of redox medicine applications. For instance, bardoxolone-methyl, a synthetic triterpenoid, is being studied for its potential therapeutic effects in diabetic kidney disease, Alport syndrome, advanced solid tumors and lymphomas, among others (Chertow et al., 2021; Hong et al., 2012; Nangaku et al., 2023). Another potential therapeutic antioxidant, resveratrol, has been shown to play a role in a plethora of pathological mechanisms (Giordo, Nasrallah, et al., 2021; Giordo et al., 2022; Giordo, Zinellu, et al., 2021; Posadino et al., 2019; Ramli et al., 2023; Shaito et al., 2020., 2023), and indeed, is currently under study for its potential role in delaying memory deterioration in patients with Alzheimer's disease as well as for cardiac remodeling in hypertensive patients (Huhn et al., 2018; Marx et al., 2018; Zheng et al., 2023). Other examples includes beta-carotene, isothiocyanate sulforaphane, GKT137831 (pyrazolopyridine dione derivative), flavonoids, and others (Bisol et al., 2020; Dao et al., 2015; Fardoun et al., 2020; Maaliki et al., 2019; Schmidt et al., 2015; Slika et al., 2022). More clinical trials are underway to test the potential utilization of therapeutic antioxidants to fight cancers, neurological disorders, as well as metabolic disorders, among others.

AUTHOR CONTRIBUTIONS

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