

# Redox Signaling as A Double-Edged Regulator: Bridging Molecular Mechanisms, Physiological Balance, Pathological Disruption, and Emerging Precision Therapies in Human Health and Disease

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## Abstract

Redox signaling has emerged as a key mechanism linking cellular metabolism with systemic physiology through controlled fluctuations of reactive oxygen and nitrogen species (ROS/RNS). Once considered merely harmful byproducts, ROS and RNS are now recognized as context-dependent messengers that regulate protein modifications, transcriptional programs, and adaptive stress responses. This review aims to synthesize current knowledge on the molecular mechanisms, physiological roles, pathological disruptions, and therapeutic opportunities of redox signaling. To achieve this, relevant literature was systematically retrieved from major scientific databases using predefined keywords and inclusion criteria to ensure comprehensive and up-to-date coverage. Under physiological conditions, redox pathways orchestrate essential processes including cell proliferation, differentiation, immune defense, metabolic adaptation, angiogenesis, and neurophysiology. When chronically imbalanced, however, these pathways shift toward pathological outcomes, contributing to cardiovascular dysfunction, neurodegeneration, cancer progression, metabolic disorders, and accelerated aging. This dual role—protective in physiological states yet detrimental under dysregulation—emerges as a unifying principle in human biology. Clinically, conventional antioxidant therapies have delivered inconsistent outcomes, while more selective strategies such as Nrf2 activators and mitochondria-targeted antioxidants show greater promise by preserving beneficial signaling while correcting pathological states. In addition, redox biomarkers are gaining relevance as tools for precision diagnostics and patient-tailored interventions. In conclusion, redox signaling functions as both a guardian of homeostasis and a driver of disease. Advancing mechanistic understanding through omics technologies and real-time biosensing is expected to unlock novel diagnostic and therapeutic strategies, reinforcing redox signaling as a central axis for precision medicine.

**Keywords:** Human health, Redox signaling, Reactive oxygen species (ROS), Reactive nitrogen species (RNS), Oxidative stress, Xidative stress–related diseases.

## Abbreviations

AP-1: Activator Protein-1;  
ARE: Antioxidant Response Element;  
ATP: Adenosine Triphosphate;  
AMPK: AMP-Activated Protein Kinase;  
ERK: Extracellular Signal-Regulated Kinase;  
GSH: Reduced Glutathione;  
GSSG: Oxidized Glutathione;  
GPx: Glutathione Peroxidase;  
HIF-1 $\alpha$ : Hypoxia-Inducible Factor-1 alpha;  
HO-1: Heme Oxygenase-1;  
IKK: I $\kappa$ B Kinase;  
Keap1: Kelch-like ECH-Associated Protein 1;  
LDL: Low-Density Lipoprotein;  
MAPK: Mitogen-Activated Protein Kinase;  
mTOR: Mammalian Target of Rapamycin;  
NADPH: Nicotinamide Adenine Dinucleotide Phosphate (reduced form);  
NF- $\kappa$ B: Nuclear Factor kappa-light-chain-enhancer of Activated B cells;  
NO: Nitric Oxide;  
NOS: Nitric Oxide Synthase;  
NOX: NADPH Oxidase;  
Nrf2: Nuclear Factor Erythroid 2-Related Factor 2;  
PI3K/AKT: Phosphatidylinositol 3-Kinase / Protein Kinase B;  
PGC-1 $\alpha$ : Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-alpha;

PKC: Protein Kinase C;  
Prx: Peroxiredoxin;  
PTEN: Phosphatase and Tensin Homolog;  
PTP: Protein Tyrosine Phosphatase;  
RNS: Reactive Nitrogen Species;  
ROS: Reactive Oxygen Species;  
SOD: Superoxide Dismutase;  
STAT: Signal Transducer and Activator of Transcription;  
Trx: Thioredoxin;  
VEGF: Vascular Endothelial Growth Factor

## Introduction

Redox signaling has been identified as one of the basic processes controlling cellular homeostasis and adaptability to changes in the environment [1]. This concept is rooted in the understanding that reactive oxygen species (ROS) and reactive nitrogen species (RNS) act not only as damaging metabolic byproducts, but also as important signaling mediators that influence a wide range of biological functions [2]. Under physiological conditions, the activity of mitochondria, NADPH oxidase, xanthine oxidase enzymes, and other enzymatic pathways produces these compounds in regulated proportions [3]. Cells can respond to both internal and exterior stimuli by using the moderate generation of ROS and RNS as second messengers in a variety of signal transduction pathways [4].

Since redox signaling controls post-translational changes of proteins, especially at oxidation-sensitive cysteine residues, its function in cell biology is extremely important [5]. Protein redox state variations can influence intermolecular interactions, enzyme activity, and protein stability, which in turn can influence how proliferation, differentiation, apoptosis, and energy metabolism are regulated [6]. Redox signaling helps coordinate physiological processes at the tissue level, such as angiogenesis, immunological response, and neuromodulatory activity [7]. Therefore, it is possible to think of the redox system as a connection between organ function regulation and cellular metabolism [8].

Despite its vital function, the fragile redox balance makes this system vulnerable to disruption. Oxidative stress is the result of ROS and RNS generation surpassing the natural antioxidant defense system's capabilities [9]. This disorder interferes with redox-dependent signaling cascades and damages

proteins, DNA, and lipids through oxidative means [10]. Consequently, redox signaling, which at first seemed protective, can become a factor that sets off the pathogenesis of a number of diseases [11]. For instance, long-term increases in ROS are linked to over-activation of inflammatory pathways through the transcription factor NF- $\kappa$ B, which helps atherosclerosis grow [12]. Similarly, the buildup of abnormal protein aggregates in neurodegenerative illnesses like Parkinson's and Alzheimer's is linked to redox dysregulation in the nervous system [13].

Fascinatingly, redox signaling displays a dualistic character in the setting of cancer. On the one hand, a limited increase in ROS can promote tumor cell proliferation and survival through activation of the MAPK and PI3K/AKT pathways [14]. However, this situation actually causes necrosis and apoptosis when ROS levels approach a particular threshold, which makes it a possible target in anticancer therapy efforts [15]. This occurrence demonstrates that redox signaling is a complex mechanism that is dependent on the oxidative stimulus's intensity, location, and duration rather than being a straightforward linear process [16].

Efforts to create therapeutic approaches based on redox modulators further reinforce the clinical relevance of redox signaling [17]. In order to address redox imbalances, a number of research are investigating the use of both conventional antioxidants and compounds that are especially directed at organelles, including mitochondria [18-20]. Furthermore, it is thought that activating the transcription factor Nrf2, which is a crucial regulator of cellular antioxidant responses, may help stop oxidative stress-induced tissue damage [21]. Since the physiological functions of ROS and the RNS cannot be

fully replaced without running the danger of upsetting normal homeostasis, the efficacy of redox-based therapies is still debatable [22].

Given this context, redox signaling becomes a crucial area of research to comprehend both from a fundamental biological standpoint and for its consequences on the pathophysiology of illness. This review aims to outline the molecular basis of redox signaling, explain its role in normal physiology, and highlight its contribution in various pathological conditions. It is anticipated that a better comprehension of this mechanism will lead to new possibilities for the creation of redox-regulated diagnostic and treatment approaches.

### Data collection method

The literature for this review was systematically collected from major scientific databases, including Scopus, Web of Science, PubMed, and ScienceDirect, covering the publication period 2000 - 2025 to capture both early developments and recent advances in the field of redox signaling. The search strategy employed a combination of keywords and Boolean operators such as “redox signaling,” “reactive oxygen species (ROS),” “reactive nitrogen species (RNS),” “oxidative stress,” “mitochondria,” “Nrf2/Keap1,” “NF- $\kappa$ B,” “MAPK,” “PI3K/AKT,” “angiogenesis,” “neurodegeneration,” “cancer,” “metabolic disorder” and “aging.” Inclusion criteria were limited to peer-reviewed original research articles and comprehensive reviews reporting empirical data or mechanistic insights on redox sources, regulatory molecules, biomolecular targets (proteins, lipids, DNA), physiological roles, pathological implications and clinical or therapeutic applications in humans or relevant preclinical models. Exclusion criteria comprised editorials, commentaries, conference proceedings, preprints without peer review, and non-English publications. The screening process was conducted in 3 stages (title, abstract, and full-text review), with duplicates removed, and supplemented by citation tracking (snowballing) to identify additional relevant studies. Data were extracted using a standardized approach, focusing on ROS/RNS sources, redox regulatory molecules, signaling pathways, physiological and pathological outcomes, and clinical implications. The synthesis was performed narratively and thematically, following PRISMA principles

adapted for narrative reviews to ensure transparency, reproducibility, and comprehensiveness in source selection.

### Molecular basis of redox signaling

Redox signaling is a cellular communication mechanism that relies on changes in oxidation–reduction status, involving the production of reactive oxygen and nitrogen species from various intracellular sources such as mitochondria and NADPH oxidase. The balance of this system is maintained by key regulatory molecules, including glutathione, thioredoxin, peroxiredoxin, catalase, and superoxide dismutase, which play a role in maintaining redox homeostasis. Redox signaling activity is further mediated through interactions with critical biomolecular targets, particularly thiol residues in proteins, membrane lipids, and DNA, thereby influencing biological function and genome stability.

### Definition of redox signaling

Redox signaling is a biological control system that bases cellular communication on alterations in oxidation-reduction status [23]. The primary mediators of this process are ROS and RNS, which are generated under control by regular metabolic processes such as nitric oxide synthase, the mitochondrial electron transport chain, and NADPH oxidase enzymes [2]. ROS and RNS function as signaling chemicals that can cause reversible changes in target proteins, especially by oxidizing cysteine residues or other thiol groups, rather than as harmful agents at low to moderate doses [24].

These redox changes affect how cellular signal transduction pathways proceed by altering protein structure, enzyme activity, or transcription factor regulation [6]. Redox signaling thus regulates a number of critical biological processes, such as immune function modulation, energy metabolism regulation, cell proliferation and differentiation, and oxidative stress adaptation [25]. Thus, redox signaling can be thought of as both a crucial point that determines the onset of pathological diseases when the oxidation–reduction equilibrium is upset and a homeostatic system that preserves physiological balance [26].

### The main sources of ROS/RNS in cells

The main sources of ROS and RNS in cells come from normal metabolic activity and specific enzymatic pathways [3]. The main contributors to the electron transport chain through electron leakage are mitochondria, specifically complexes I and III, which generate superoxide as a consequence of aerobic respiration [27]. Apart from mitochondria, the NADPH oxidase (NOX) enzyme is a crucial regulator of ROS that is involved in immunological defense mechanisms in phagocytic cells and physiological signaling in non-phagocytic cells [28]. Moreover, lipoxygenase, cyclooxygenase, and xanthine oxidase aid in the production of ROS, especially when purine metabolism and inflammatory pathways are involved [29].

The primary chemical in RNS is nitric oxide (NO), which is generated by the enzymes in the nitric oxide synthase (NOS) family [30]. NO is a key mediator in immune response control, synaptic transmission, and vasodilation [31]. Nevertheless, in some circumstances, NO and superoxide can combine to generate peroxynitrite, a very reactive RNS that may result in oxidative damage [32]. Therefore, ROS/RNS that physiologically promote cellular signaling are primarily produced by mitochondria, NADPH oxidase, and other redox enzymes. However, if production surpasses the antioxidant defense system's capacity, oxidative stress may result [33].

### Key molecules in redox regulation

The fundamental defense mechanism for preserving the oxidation-reduction balance inside cells is provided by key chemicals involved in redox control [34]. Among the most crucial elements is glutathione (GSH), a tripeptide that works with glutathione disulfide (GSSG) in the oxidation–reduction cycle to act as a redox buffer [35]. High cytoplasmic GSH concentrations enable cells to directly neutralize ROS while preserving a reductive intracellular environment [36].

Furthermore, the decreased status of cysteine residues in target proteins is maintained in part by the thioredoxin (Trx) system [37]. Thioredoxin and the enzyme thioredoxin reductase can restore oxidized proteins to their active state and control the activity of transcription factors that are redox-sensitive [38]. The antioxidant enzyme peroxiredoxin (Prx), which breaks

down peroxides with remarkable sensitivity, functions in concert with this system [39]. In addition to being a detoxifier, peroxiredoxin is a redox sensor that can communicate oxidative signals to other molecular processes [40].

Another important component is superoxide dismutase (SOD), which catalyzes the conversion of superoxide to hydrogen peroxide [41]. Catalase or glutathione peroxidase then breaks down this product into water and oxygen, avoiding the buildup of potentially harmful peroxides [42]. These molecules work together to create a dynamic defense network that controls the strength and duration of redox signals in addition to neutralizing reactive species [43].

### Redox biomolecule targets

Redox signaling primarily targets biological macromolecules, including proteins, lipids, and DNA, that are susceptible to shifts in their oxidation-reduction condition [44]. Targeting proteins is crucial, particularly cysteine residues with reactive thiol groups [45]. Reversible oxidation of the thiol group can result in various modifications, such as disulfide bridge formation, S-nitrosylation, or S-glutathionylation [46]. The control of signal transduction pathways is directly impacted by these alterations in protein shape, enzymatic activity, and interprotein interactions [47]. For instance, oxidation of specific cysteine residues can change the kinetics of protein phosphorylation in the PI3K/AKT and MAPK pathways by activating or deactivating phosphatases [48].

In addition to proteins, lipids in membranes are also prone to oxidation, particularly polyunsaturated fatty acids (PUFA), which are sensitive to lipid peroxidation [49]. Products of lipid peroxidation, such 4-hydroxy-nonenal (4-HNE) and malondialdehyde (MDA), serve as supplementary signal mediators in addition to indicating the existence of oxidative damage [50]. These compounds have the ability to attach to proteins and affect molecular function, such as by causing stress genes to be expressed or inflammatory pathways to be activated [51]. As a result, oxidative lipids have two functions: They regulate cell adaptability and serve as a damage indicator [49].

DNA is another important target because the nucleotide bases can be oxidatively modified [52]. One

of the most well-known types is the production of 8-hydroxy-2'-deoxyguanosine (8-oxo-dG), which might result in mutations if DNA repair mechanisms don't fix it right away [53]. Apart from its mutagenic effects, oxidative stress-induced DNA damage also acts as a signal to trigger the DNA damage response system, which impacts senescence, apoptosis, or the cell cycle

[54]. In this sense, redox signals can influence DNA interactions to decide a cell's fate under stress [44].

Figure 1 shows the molecular basis of redox signaling, including the main intracellular sources of ROS and RNS, the key regulatory molecules that maintain redox homeostasis, and the primary biomolecular targets such as proteins, lipids, and DNA.

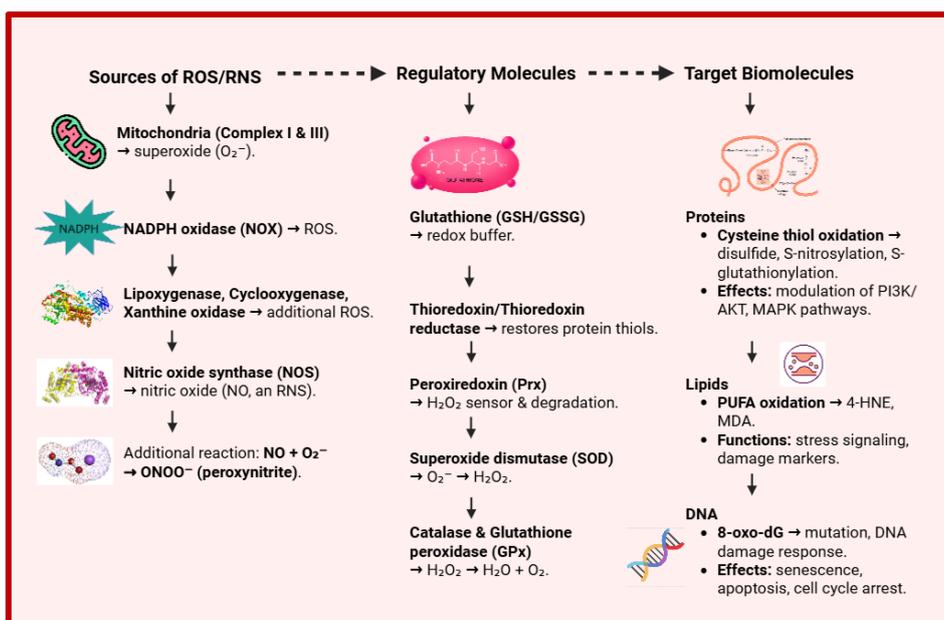


Figure 1 Molecular basis of redox signaling and its regulatory network.

**Redox signaling in normal physiology**

Redox signaling plays a crucial role in maintaining biological function through several key mechanisms. First, it regulates cell proliferation and differentiation by modulating the activity of transcription factors and signaling pathways that direct cell growth and specialization. Second, redox signaling plays a role in immune function and the inflammatory response, both by activating phagocytic cells to kill pathogens and by controlling the release of inflammatory mediators. Third, this mechanism contributes to the regulation of energy metabolism, particularly through the control of mitochondrial

oxidation and bioenergetic processes that ensure balanced ATP production. Fourth, redox signaling also supports adaptive responses to stress (redox hormesis), where exposure to low levels of ROS can trigger protective mechanisms that enhance cell resilience to oxidative challenges. Fifth, redox pathways are involved in angiogenesis, cardiovascular function, and neurophysiology, thus playing a crucial role in maintaining tissue integrity, regulating blood circulation, and nervous system activity. Table 1 shows that redox signaling is a multifunctional regulatory mechanism in normal physiology.

Table 1 Role of redox signaling in normal physiology.

Physiological aspects	Main mechanism	Biological impact	Related molecules/pathways	Reference
Cell proliferation and differentiation	Reversible oxidation of cysteine residues in protein phosphatases	Regulates cell division, tissue growth, and direction of stem cell	Physiological ROS, MAPK, and ERK	[58]

Physiological aspects	Main mechanism	Biological impact	Related molecules/pathways	Reference
	→ MAPK/ERK activation	differentiation		
Immune and inflammatory function	Respiratory burst of phagocytes by NADPH oxidase; modulation of T cell activation	Elimination of pathogens, regulation of cytokines, and prevention of excessive inflammation	ROS, NO, and NADPH oxidase	[67]
Energy metabolism	Mitochondrial ROS as a retrograde signal to the nucleus; activation of AMPK/PGC-1 $\alpha$	Mitochondrial biogenesis, increased efficiency of energy oxidation, and metabolic adaptation	Mitochondrial ROS, AMPK, and PGC-1 $\alpha$	[77]
Stress adaptation (redox hormesis)	Nrf2 activation by low dose ROS → induction of antioxidant enzymes	Increased protective capacity of cells against oxidative stress	Nrf2, HO-1, and GPx	[86]
Angiogenesis and cardiovascular function	ROS stabilize HIF-1 $\alpha$ ; NO mediates vasodilation	Stimulation of angiogenesis and blood pressure regulation	ROS, HIF-1 $\alpha$ , and NO	[95]
Neurophysiology	Modulation of synaptic transmission and neuronal plasticity by ROS/NO	Memory regulation, learning, and synapse function	ROS, NO, and synaptic pathways	[98]

### Regulation of cell proliferation and differentiation

Redox signaling is a crucial process that modifies intracellular signaling pathways and controls transcription factor activity to control cell proliferation and differentiation [10]. Physiological ROS are signaling molecules that can affect protein-protein interactions, the redox state of cysteine residues, and protein phosphorylation [55,56]. This method enables the control of gene expression linked to cell growth, maturation, and the cell cycle [57].

The MAPK/ERK and PI3K/AKT pathways, which are crucial for promoting cell cycle progression, can be activated by ROS at moderate concentrations in the context of proliferation [58]. Cell proliferation can be regulated when this pathway is activated because it enhances the transcription of genes that support DNA synthesis and the G1 to S phase transition [59]. On the other hand, too many ROS can damage DNA and activate pro-apoptotic pathways, which actually prevents cell division or causes cell death [60].

Redox signaling has a more intricate function in the differentiation process. For instance, transient ROS are necessary for myoblast development into muscle fibers in order to activate transcription factors like NFAT and MyoD [61]. Redox balance also affects the differentiation of hematopoietic stem cells; low ROS levels preserve the ability to self-renew, whereas high ROS levels encourage differentiation in the direction of the myeloid pathway [62].

Furthermore, redox-sensitive transcription factors including HIF-1 $\alpha$ , Nrf2, and NF- $\kappa$ B are essential for striking a balance between the demands of differentiation and proliferation [63]. Cells can react quickly and adaptably to oxidative stressors because to the redox switches that are reversibly modified cysteine residues in cell cycle regulating proteins [64].

### Immune function and inflammatory response

ROS and RNS work as signal mediators that synchronize immune cell activity, and redox signaling is essential for immune function and the control of

inflammatory responses [4]. The ROS produced by NADPH oxidase during the respiratory burst is used by phagocytic cells, including neutrophils and macrophages, to eliminate ingested pathogens [65]. This procedure validates that ROS are essential elements in the body's fight against infection as well as metabolic byproducts [66].

Apart from their direct antimicrobial functions, ROS and RNS also affect lymphocyte proliferation and differentiation, modify cytokine and chemokine production, and regulate T and B cell activity [67]. Redox state plays a crucial role in the activation of transcription factors like NF- $\kappa$ B in immune cells. Reversible oxidation of cysteine residues causes NF- $\kappa$ B to translocate to the nucleus, where it induces the production of defensive and inflammatory genes [68,69]. In the meantime, Nrf2 activation in immune cells serves as a defense mechanism, preventing tissue damage from excessive inflammation by balancing the creation of ROS with the stimulation of antioxidant enzymes [70].

Inflammation resolution also heavily relies on redox signaling. Early-produced ROS in the immune response can activate pro-resolving pathways and release anti-inflammatory mediators, which can help reduce inflammation once the pathogen is defeated [33]. However, redox dysregulation can lead to tissue damage, chronic inflammation, and the etiology of chronic diseases like diabetes, autoimmune diseases, and atherosclerosis. It can manifest as inadequate antioxidant capacity or chronic ROS accumulation [71].

### Regulation of energy metabolism

Redox signaling is essential for controlling energy metabolism, mostly by adjusting cellular bioenergetic pathways and mitochondrial activity [72]. The primary source of ROS generation during oxidative phosphorylation is the mitochondria [73,74]. At the physiological level, these ROS serve as signaling molecules that control the balance of energy within cells in addition to being regarded as metabolic byproducts [75].

Retrograde signals from mitochondrial ROS can affect nuclear genes involved in mitochondrial metabolism and biogenesis [76]. ROS-induced activation of pathways including AMPK and PGC-1 $\alpha$

promotes cells' enhanced oxidative capacity, improves mitochondrial biogenesis, and maximizes the efficiency of ATP synthesis [77]. Cells can therefore modify their energy output in response to environmental factors and physiological demands [78]

Furthermore, redox signaling coordinates substrate oxidation, glucose metabolism, and fatty acid oxidation by interacting with other energy sensors like as NAD<sup>+</sup>/NADH and SIRT1 [79]. Controlled redox changes enable cells to adjust to shifting nutrient levels without being overly stressed by oxidation [80].

Redox imbalances can affect mitochondrial function, reduce the effectiveness of oxidative phosphorylation, and raise the risk of metabolic dysfunction. Examples of these imbalances include chronic ROS buildup or diminished antioxidant capacity [81]. This condition contributes to the development of chronic metabolic diseases, including type 2 diabetes, obesity, and insulin resistance [63].

### Stress adaptation signals

Redox signaling is essential to redox hormesis, an adaptive process whereby exposure to low to moderate concentrations of ROS or RNS triggers the cell's defenses [82]. According to the hormesis concept, ROS are not always harmful; at physiological concentrations, they function as second messengers that activate cellular defense mechanisms and boost resistance to oxidative stress in the future [83,84].

Redox hormesis occurs at the molecular level through the activation of transcription factors like Nrf2, which separates from Keap1 upon oxidation of cysteine residues [85]. Then, Nrf2 moves to the nucleus of the cell and triggers the production of genes related to detoxification and antioxidant defense, such as heme oxygenase-1, glutathione peroxidase, and superoxide dismutase [86]. This pathway's activation improves cell viability, decreases biomolecular damage, and fortifies the cell's defenses against excessive ROS [21].

Apart from Nrf2, the redox hormesis pathway also affects PI3K/AKT and MAPK, which are involved in cell homeostasis, differentiation, and proliferation [87]. Low quantities of transient ROS can cause significant proteins to become phosphorylated without permanently harming cells, enabling them to adjust to shifting metabolic or environmental stressors [88].

Numerous biological systems, such as immune cells, neurons, and skeletal muscle, have been shown to exhibit redox hormesis. This suggests that the adaptation is an evolutionary tactic to boost resistance to long-term oxidative stress [89]. On the other hand, cell malfunction, inflammation, and degenerative illnesses can result from a breakdown of the hormesis mechanism brought on by excessive oxidative stress or a disturbance of the redox sensor pathway [82].

#### **Role in angiogenesis, cardiovascular function, and neurophysiology**

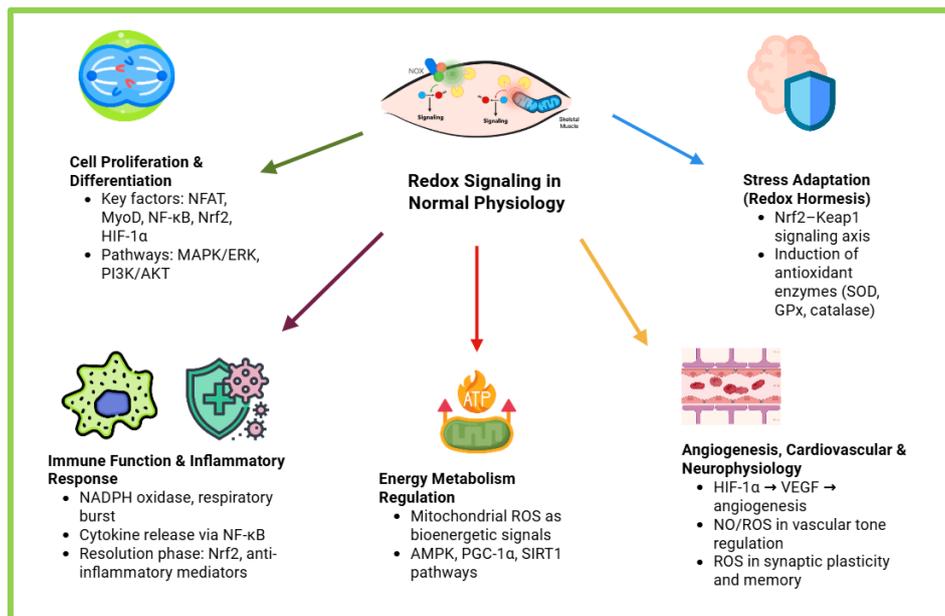
Through the regulation of ROS and RNS as signal mediators, redox signaling plays a significant role in angiogenesis, cardiovascular function, and neurophysiology [90]. ROS serve as a signal that stabilizes the transcription factor hypoxia-inducible factor 1 $\alpha$  (HIF-1 $\alpha$ ) throughout the angiogenesis process [91]. Vascular endothelial growth factor (VEGF), which encourages endothelial proliferation, cell migration, and the development of new blood vessels, is one of the pro-angiogenic genes that are stimulated by HIF-1 $\alpha$  activation [92]. This mechanism allows tissues to adapt to hypoxia and increased metabolic demands [93].

Through the interplay of ROS and NO, redox signaling controls blood pressure regulation and vascular tone in cardiovascular function [94]. Moderate ROS contribute to the modulation of NO activity and vascular signal transmission, whereas NO, which is produced by the endothelium, is a significant vasodilator [95,96]. Chronic ROS buildup and other forms of redox dysregulation can reduce NO bioavailability, which can result in atherosclerosis, hypertension, and endothelial dysfunction [97].

RNS and ROS have an impact on synaptic transmission, neural plasticity, and cognitive function from a neurophysiological perspective [98]. The long-term potentiation (LTP) processes that underpin learning and memory, ion channel activity, and neuronal excitability can all be altered by ROS at physiological levels [99]. Neuroprotective gene expression and adaptive reactions to oxidative stress are likewise regulated by redox pathway activation [17]. Conversely, excessive accumulation of ROS/RNS can lead to synaptic damage, mitochondrial dysfunction, and neuronal death, which are associated with neurodegeneration such as Alzheimer's and Parkinson's [100].

As depicted in **Figure 2**, redox signaling acts as a central mechanism connecting cellular growth, immune defense, energy regulation, and systemic functions.

Although the role of redox signaling in proliferation, immunomodulation, energy metabolism, stress adaptation, and systemic functions is well established, the underlying mechanisms remain only partially understood. The narrow threshold between physiological ROS signaling and oxidative damage indicates the presence of molecular controls more refined than currently recognized. Variability in antioxidant capacity across individuals suggests genetic and epigenetic determinants influencing susceptibility to redox imbalance. Emerging hypotheses also point to redox signaling as an integrative communication hub linking metabolic state, circadian rhythm, and epigenetic regulation. These perspectives open new directions for exploring normal physiology and may provide the foundation for strategies aimed at enhancing resilience to oxidative stress.



**Figure 2** Schematic illustration of the roles of redox signaling in normal physiology.

**Redox signaling in pathological conditions**

Redox dysregulation and chronic oxidative stress play a central role in various pathological conditions, including cardiovascular diseases such as atherosclerosis and hypertension, neurodegenerative diseases such as Alzheimer’s and Parkinson’s, and cancer, which exhibit a dualistic nature between the promotion of proliferation and the induction of apoptosis; in addition, redox imbalance also contributes

to metabolic disorders such as diabetes and obesity, as well as accelerating the aging process and the onset of age-related diseases, confirming that redox balance is a key factor in maintaining cellular integrity and preventing pathology. **Table 2** highlights how redox signaling, which is beneficial under physiological conditions, can become a pathological mechanism when the redox balance is disturbed.

**Table 2** Role of redox signaling in pathological conditions.

Pathological conditions	Main mechanism	Biological impact	Related molecules/pathways	Reference
Chronic oxidative stress	Increased ROS/RNS, decreased antioxidant capacity	Protein, lipid, and DNA damage → molecular basis of degenerative diseases	ROS, RNS, and antioxidant enzymes	[101]
Cardiovascular disease	LDL oxidation → foam cell formation; endothelial dysfunction due to decreased NO	Atherosclerosis, hypertension, and decreased vascular elasticity	Oxidized LDL, NO, and NADPH oxidase	[109]
Neurodegenerative diseases (Alzheimer’s and Parkinson’s)	Mitochondrial dysfunction, oxidation of synaptic proteins and lipids, and mt DNA damage	Abnormal protein aggregation, energy failure, and neuronal death	ROS, RNS, mtDNA, and synaptic proteins	[117]
Cancer	Activation of proliferative pathways	Tumor cell proliferation and	ROS, MAPK, PI3K/AKT, and DNA	[124]

Pathological conditions	Main mechanism	Biological impact	Related molecules/pathways	Reference
	(MAPK and PI3K/AKT) by ROS; high ROS accumulation triggers apoptosis	survival; redox-based therapeutic targets		
Metabolic disorders (diabetes and obesity)	Hyperglycemia → increased mitochondrial ROS and PKC activation	Insulin resistance, adipose tissue inflammation, and vascular complications	Mitochondrial ROS, PKC, and insulin signaling	[134]
Aging and age-related diseases	Decreased endogenous antioxidants; progressive oxidative damage to biomolecules	Tissue dysfunction, accelerated aging, and increased risk of chronic disease	ROS, endogenous antioxidants, and free radical theory	[144]

### Chronic oxidative stress and redox dysregulation

The state known as chronic oxidative stress occurs when the generation of ROS and RNS surpasses the antioxidant defense capabilities of the cell, leading to a permanent redox imbalance [101]. ROS and RNS are signaling chemicals that regulate immunological responses, energy consumption, differentiation, and proliferation under physiological settings [3]. Nevertheless, when this equilibrium is upset, the buildup of ROS/RNS can result in biomolecular harm, such as protein carbonylation, membrane lipid oxidation, and DNA damage and mutation [2].

Cell and tissue dysfunction is made worse by chronic redox dysregulation, which sets off a prolonged activation of stress and inflammatory pathways, such as NF- $\kappa$ B, MAPK, and pro-apoptotic pathways [102]. This results in atherosclerosis, hypertension, and endothelial dysfunction in cardiovascular tissue [103]. Chronic oxidative stress is a key pathogenic factor in neurodegenerative illnesses because it causes mitochondrial malfunction, abnormal protein aggregation, and neuronal death in the nervous system [104,105]. The underlying cause of metabolic diseases including diabetes and obesity, redox dysregulation also impacts cell metabolism, exacerbates insulin resistance, and causes chronic inflammation in adipose tissue [106].

This occurrence demonstrates that redox imbalance plays a significant role in connecting oxidative stress to chronic disease and is not just a byproduct of cellular metabolism [63]. Therefore, it is essential to comprehend the processes of oxidative stress and redox control in order to design therapeutic techniques that directly target redox balance, either by using targeted antioxidants or by activating protective pathways like Nrf2.

### Cardiovascular disease

Atherosclerosis and hypertension are two cardiovascular illnesses that are examples of pathologies where redox dysregulation is a major factor [107]. Under typical circumstances, ROS serve as signaling molecules that control blood pressure homeostasis, endothelial cell proliferation, and vascular tone [90]. The redox balance can be upset and oxidative stress in vascular tissue can result from long-term increases in ROS brought on by risk factors such as obesity, hypertension, or hyperlipidemia [108].

Excess ROS leads to the oxidation of low-density lipoprotein (LDL) in atherosclerosis, which in turn induces the production of foam cells in the artery wall, the activation of macrophages, and the release of inflammatory mediators [109,110]. Atherosclerotic plaques grow more quickly when transcription factors like NF- $\kappa$ B are activated because they increase the expression of endothelial adhesion molecules and pro-

inflammatory cytokines, which intensifies the inflammatory response [111]. Furthermore, ROS cause endothelial dysfunction by decreasing the bioavailability of NO, which is crucial for vasodilation [112].

ROS increase peripheral vascular resistance and arterial smooth muscle contractility in hypertension by interacting with vascular ion channels and the renin-angiotensin system [113]. This redox imbalance causes chronic vascular remodeling and exacerbates hypertension [114]. The detrimental impact of hypertension is increased when ROS buildup triggers the MAPK and PI3K/AKT pathways, which encourage the proliferation of smooth muscle cells and vascular fibrosis [115].

### Neurodegenerative disease

Redox dysregulation and the buildup of persistent oxidative stress are directly linked to neurodegenerative illnesses including Parkinson's and Alzheimer's [116]. ROS and RNS are signaling chemicals that affect synaptic transmission, neural plasticity, and the expression of neuroprotective genes in a healthy nervous system [117]. However, excessive accumulation of ROS/RNS due to environmental stressors, reduced antioxidant capacity, or mitochondrial metabolic abnormalities results in biomolecular damage that sets off neurological pathogenesis [99].

Oxidative stress has a role in Alzheimer's disease by causing beta-amyloid protein to aggregate and tau protein to be abnormally phosphorylated, which impairs synaptic function and results in neuron death [118]. In addition, excessive ROS worsens brain tissue degeneration, raises the synthesis of pro-inflammatory cytokines, and causes chronic microglial inflammation [119,120]. Stress transduction pathways including MAPK and the transcription factor NF- $\kappa$ B are activated, which increases neuronal death and inflammatory responses and speeds up the course of disease [121].

In Parkinson's disease, ROS produced by the substantia nigra's mitochondria lead to abnormal  $\alpha$ -synuclein aggregation and dopaminergic degeneration via lipid and protein oxidation [122]. Parkinson's disease-like motor symptoms are brought on by this redox disruption, which also lowers dopamine levels

and leads dopaminergic neurons to undergo apoptosis [123].

### Cancer

ROS and RNS can both promote the growth of cancer cells and induce apoptosis, demonstrating the dualistic and complex role of redox signaling in cancer [60]. ROS act as signaling molecules at physiological to moderate levels, activating proliferative pathways such as PI3K/AKT, NF- $\kappa$ B, and MAPK/ERK, which support anabolic metabolism, the cell cycle, and the survival of cancer cells [124,125]. This pathway's activation promotes angiogenesis, tumor growth, and the capacity of cancer cells to spread to neighboring tissues [126].

However, when ROS buildup exceeds the antioxidant defense capabilities of the cell, it can damage proteins, lipids, and DNA, which sets off the mechanisms of necrosis or apoptosis in cancer cells [127]. ROS functions as a "double-edged sword" in regulating tumor growth through the activation of pro-apoptotic pathways such p53, caspase, and mitochondrial membrane permeability [128].

This dichotomy highlights how crucial controlled redox homeostasis is for cancer cells; too low ROS can prevent cell division, while too high ROS can cause cell death [129]. Thus, redox-based treatment approaches are being investigated to target the crucial redox range of cancer cells. These approaches include the use of selective pro-oxidants or modulators of endogenous antioxidant mechanisms [130].

### Metabolic disorders

One important mechanism connecting the pathophysiology of diabetes mellitus and obesity to persistent oxidative stress is redox dysregulation [131]. The insulin pathway and cellular energy sensors like AMPK are activated by ROS, which under normal circumstances function as signaling molecules in the control of glucose and lipid metabolism [132]. However, oxidative damage to proteins, lipids, and DNA results from an excessive buildup of ROS brought on by insulin resistance, excessive feeding, or mitochondrial dysfunction. This impairs cellular activity in metabolic tissues [133].

Oxidative stress contributes to insulin resistance in type 2 diabetes by oxidizing cysteine residues in

important insulin signaling pathway components, such as IRS-1 and PI3K/AKT [134,135]. This condition raises hyperglycemia, decreases the transfer of glucose to muscle cells and adipocytes, and causes inflammatory cytokines to be released from adipose tissue [136]. Moreover, elevated ROS harms the vascular endothelium, hastening the development of micro- and macrovascular problems that frequently affect diabetes patients [137].

Chronic inflammation in adipose tissue is brought on by endoplasmic reticulum (ER) stress and increased NADPH oxidase activity, which are both exacerbated by visceral lipid buildup in obesity [138]. Systemic metabolic balance is disturbed and insulin resistance is made worse by this inflammation and oxidative stress. Steatosis and liver failure can also be brought on by redox dysregulation in hepatocytes [139].

#### **Aging and age-related diseases**

Redox dysregulation has a direct impact on the emergence of age-related illnesses and the cellular aging process [140]. ROS and RNS build up as people age because of mitochondrial malfunction and a decline in endogenous antioxidant activity [141]. This disorder reduces cellular integrity and tissue regenerative potential by gradually damaging proteins, lipids, and DNA [142]. This phenomenon, which is one of the primary mechanisms of cellular aging, is called oxidative damage accumulation [143].

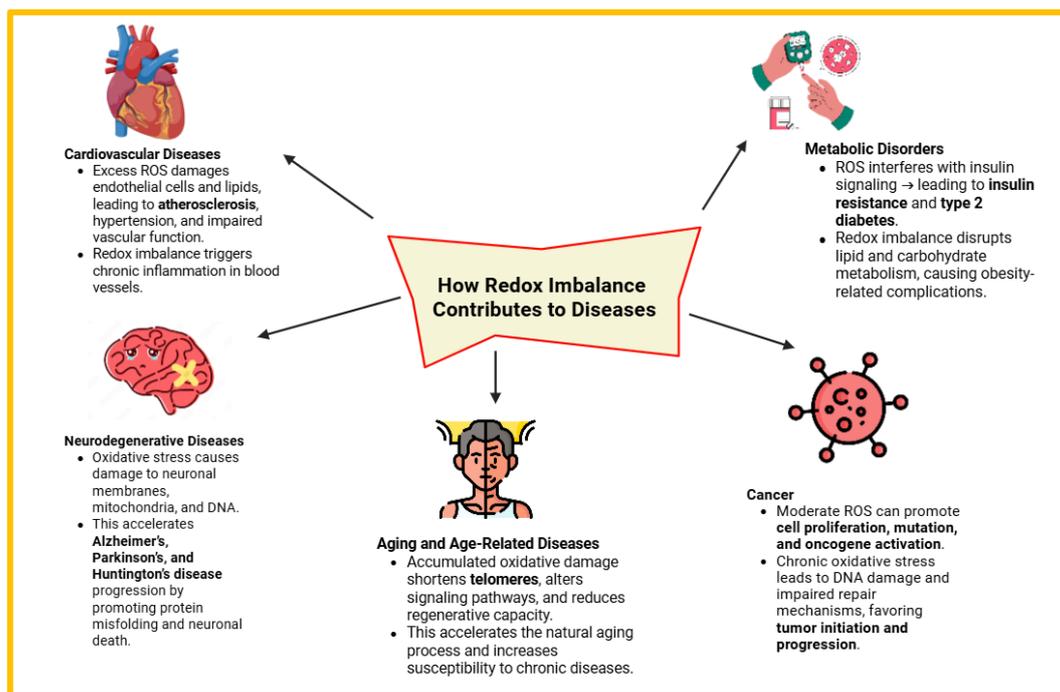
At the molecular level, too much ROS triggers stress signaling pathways that are involved in energy metabolism, apoptosis, and chronic inflammation, including as NF- $\kappa$ B, p53, and mTOR [17]. This chronic activation of inflammatory pathways, called inflammaging, contributes to the development of various degenerative diseases, such as atherosclerosis, type 2 diabetes, osteoarthritis, and neurodegenerative disorders [144]. Decreased activation of beneficial redox pathways, such Nrf2, also makes tissues more vulnerable to damage, worsens oxidative stress, and

lowers the production of endogenous antioxidant enzymes [145].

Additionally, redox dysregulation impacts mitochondrial function, increasing the rate at which mitochondrial DNA mutations accumulate and decreasing the effectiveness of cellular energy production, both of which contribute to the organ's declining physiological capacity [146]. Redox signaling is therefore essential as a mediator between the onset of age-related illnesses and the physiological aging process [147]. Redox modulation-focused therapeutic approaches, such as Nrf2 activation, endogenous antioxidant capacity augmentation, or pharmacological and nutritional therapies that reduce ROS, may slow down the aging process of cells and lessen the risk of degenerative illnesses [148].

**Figure 3** shows how chronic oxidative stress and redox dysregulation contribute to major pathological conditions, including cardiovascular diseases, neurodegenerative disorders, cancer, metabolic disorders, and aging.

Despite extensive evidence linking chronic redox dysregulation to pathological conditions, critical gaps remain in understanding the temporal dynamics, tissue specificity, and molecular thresholds that determine whether redox signaling exerts protective or deleterious effects. Emerging hypotheses propose that disease progression is influenced not only by the absolute levels of ROS/RNS but also by the oscillatory patterns and compartmentalized signaling within subcellular organelles such as mitochondria, peroxisomes, and the endoplasmic reticulum. Furthermore, increasing attention is being given to the role of redox-dependent epigenetic modifications and intercellular redox communication in shaping disease trajectories. These perspectives highlight the need to move beyond the linear concept of oxidative stress toward a systems-level framework that integrates redox signaling as a dynamic regulator of pathological processes.



**Figure 3** Redox imbalance in pathological conditions.

### Redox adaptation and regulation mechanisms

Understanding the mechanisms of redox adaptation and regulation emphasizes that reactive species do not act in isolation, but rather through complex signaling networks involving redox-sensitive transcription factors, molecular cross-pathway interactions, and the presence of redox switches on sensor proteins.

#### The role of redox-sensitive transcription factors

The redox signaling method relies heavily on redox-sensitive transcription factors, which can recognize changes in the oxidation status of cells and convert them into the proper genetic responses [149]. The balance between physiological function and preventing pathological damage is maintained by a number of important factors, including NF- $\kappa$ B, Nrf2, HIF-1 $\alpha$ , and AP-1 [150].

Nuclear factor kappa B (NF- $\kappa$ B) is activated through oxidation of key residues in the I $\kappa$ B kinase (IKK) pathway, thereby allowing translocation of NF- $\kappa$ B into the cell nucleus [151]. This activation induces the expression of various genes that play a role in inflammation, proliferation, and the adaptive immune response [152]. In a physiological context, NF- $\kappa$ B ensures an effective immune response, but chronic

activation due to oxidative stress can lead to persistent inflammation [153].

On the other hand, nuclear factor erythroid 2-related factor 2 (Nrf2) protects by controlling the expression of genes involved in detoxification and antioxidant defense. When Nrf2 is at rest, it attaches itself to Keap1 and is broken down by proteases [154]. Cysteine residues on Keap1 are oxidized by increased ROS, which causes Nrf2 to go to the nucleus and activate the antioxidant response element (ARE) [155]. This pathway's activation boosts the synthesis of antioxidant enzymes that fortify the cell's defenses, including heme oxygenase-1 and glutathione peroxidase [156].

Inducible factor for hypoxia ROS and oxygen control the transcription factor 1 $\alpha$  (HIF-1 $\alpha$ ) [157]. Proline hydroxylation by prolyl hydroxylase causes HIF-1 $\alpha$  to be degraded by proteasomes under normoxia [158]. However, elevated ROS under hypoxia prevents this breakdown, enabling HIF-1 $\alpha$  to promote the production of VEGF and other pro-angiogenic genes that are critical for vascular adaptation [159].

On the other hand, ROS activates activator protein-1 (AP-1), which is made up of the dimer of the Fos and Jun proteins, via the MAPK pathway [4]. AP-1 activation plays a role in cell proliferation, differentiation, and response to stress [160]. Similar to

other transcription factors, AP-1 has a contextual role; while it is advantageous in physiological settings, excessive activation can lead to pathological processes like cancer [161].

#### **Crosstalk with other signal paths**

Redox signaling interacts with a number of different signal transduction pathways, including MAPK, PI3K/AKT, and JAK/STAT, that control cellular activity rather than operating independently [162]. A dynamic and intricate signaling network is created by these interactions, enabling cells to react to pathogenic stress and different physiological inputs in an adaptive manner [163].

ROS contributes to the regulation of kinase activation in the mitogen-activated protein kinase (MAPK) pathway by reversibly oxidizing cysteine residues in protein phosphatases [22]. This oxidation prolongs the activation of ERK, JNK, or p38 MAPK by inhibiting phosphatase activity [164]. These processes play a key role in regulating differentiation, proliferation, and stress response. On the other hand, prolonged inflammation or apoptosis may result from excessive activation brought on by chronic oxidative stress [165].

ROS contribute to the PI3K/AKT pathway by deactivating PTEN, a phosphatase that typically suppresses PI3K [166]. Oxidation-induced PTEN inactivation raises AKT activation, which promotes cell survival, proliferation, and metabolic control [167]. The dualistic nature of redox signaling is illustrated by this interaction, which can promote cell viability at normal levels while also aiding in the transformation of cancer cells through enhanced proliferation and resistance to apoptosis in pathological settings [168].

In the meantime, tyrosine kinases and phosphatases that regulate STAT phosphorylation are modulated by redox signaling in the JAK/STAT channel [169]. ROS can increase STAT phosphorylation, which in turn can induce the production of genes linked to inflammation, differentiation, or proliferation, hence amplifying cytokine signals [17]. The immune response depends on these interactions, but if they are dysregulated, as they are in autoimmune disorders or chronic inflammation, they can also worsen pathological conditions [125].

#### **The concept of redox switches in sensor proteins**

Redox switches in sensor proteins describe how reversible modifications of amino acid residues, especially cysteine, can transform shifts in cellular redox state into chemical signals [170]. Thiol groups (-SH) found in cysteine residues are extremely reactive with ROS and RNS [171]. These thiol groups can undergo oxidation under physiological conditions, leading to a variety of modifications, including intramolecular disulfides, S-nitrosylation, S-glutathionylation, and sulfenylation [172]. These chemical alterations serve as molecular switches that control how proteins interact with other molecules and how active they are [172].

One such illustration is the control of the protein tyrosine phosphatase (PTP) enzyme [173]. Tyrosine phosphorylation builds up and proliferative signaling in the MAPK or PI3K/AKT pathways is prolonged when PTP activity is momentarily blocked by oxidizing catalytic cysteine residues [174]. This process demonstrates how reversible oxidation functions as a switch to control the signal's strength and duration [175].

Furthermore, redox switches are used by sensor proteins like Keap1 in the Nrf2 system to identify elevated ROS [176]. Keap1 cysteine oxidation modifies protein structure, releases Nrf2, and permits the expression of antioxidant genes [177]. Peroxiredoxin and hemoglobin are two other examples, both of which employ redox modification to modify their functions in response to oxidative stressors [178].

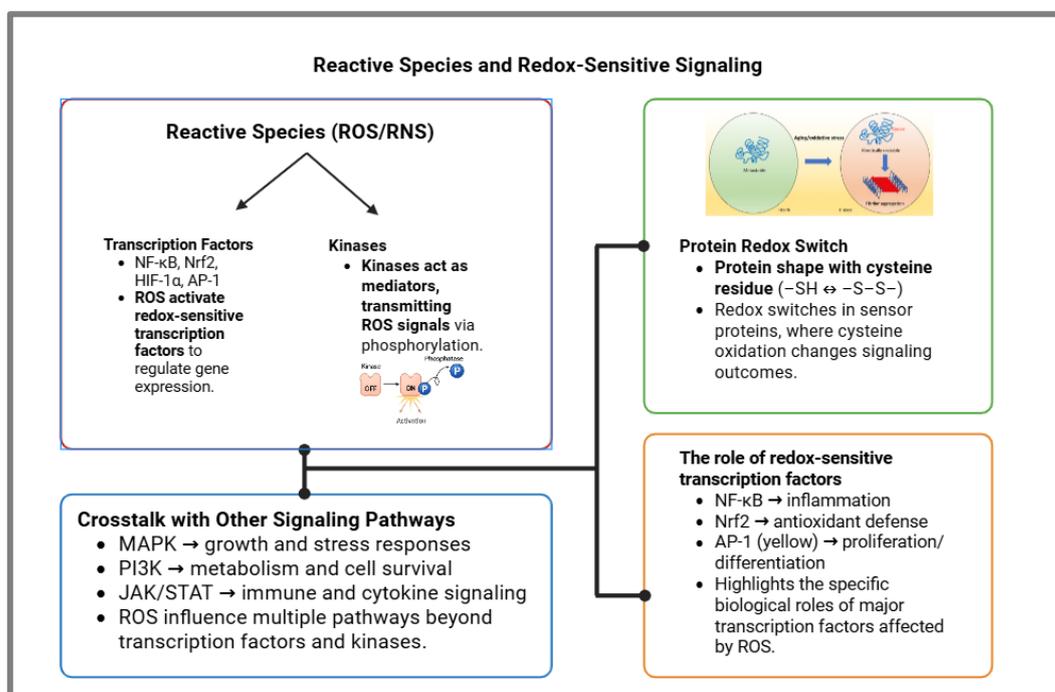
This redox switch system's dynamic and reversible nature is a benefit. Reversible redox alterations, as opposed to irreversible oxidative damage, enable proteins to act as sensors that are both sensitive and adaptable to changes in the cellular environment [44]. Redox switches thus emerge as a key mechanism that connects adaptive physiological responses to the oxidation status of cells [179].

However, reversible alterations, like the creation of sulfinates or sulfonates at cysteine residues, might turn into irreversible changes if exposure to ROS or RNS is sufficient [180]. Protein function is permanently lost in this situation, which also serves as the molecular foundation for a number of clinical

disorders, including as cancer, neurodegeneration, and aging [64].

**Figure 4** depicts how redox regulation integrates transcriptional control, signaling pathway crosstalk,

and sensor protein modifications to maintain cellular homeostasis and guide therapeutic implications.



**Figure 4** Redox adaptation and regulation mechanisms.

### Clinical and therapeutic implications

Although there are still many obstacles to overcome, an understanding of redox signaling has created a wealth of prospects for the development of treatment interventions. Conventional antioxidant-based approaches were initially considered promising for reducing the impact of oxidative stress in various degenerative diseases [181]. However, clinical results show controversial effectiveness, largely because non-specific antioxidants are unable to distinguish between beneficial physiological redox signals and damaging pathological ROS/RNS [36]. Consequently, in extensive clinical studies, these treatments frequently fall short of offering steady benefits. **Table 3** summarizes various approaches in the application of redox signaling in the clinical field.

On the other hand, particular redox modulator tactics that target particular biochemical pathways are now being development [182]. Nrf2 activators, such sulforaphane and bardoxolone methyl, are intended to boost the expression of detoxification and antioxidant genes in order to improve the natural protective

response [183]. Furthermore, mitochondria-specific antioxidants like MitoQ and SkQ1 have been created to inhibit the primary ROS generator without impairing the physiological role of redox signaling [20]. This strategy has demonstrated more focused outcomes and may lessen the negative effects of traditional antioxidant treatment [184].

Redox status biomarkers are starting to be employed in the diagnostic field to track illness symptoms and evaluate prognosis [185]. The degree of oxidative stress and the patient's potential for antioxidant defense can be shown by markers such the GSH/GSSG ratio, protein carbonyls, or lipid oxidation products (malondialdehyde) [186]. It is anticipated that this biomarker would improve the precision of diagnosis, forecast the course of the disease, and direct redox-based treatment [187].

In the future, the prospects for redox signaling-based therapies are expected to grow further along with a better understanding of the crosstalk of redox pathways with other signaling systems [188]. Targeting particular redox components in patient subgroups

through precision medicine therapy may maximize benefits while lowering hazards [189]. Combination strategies are also being investigated to improve therapy efficacy, such as the use of Nrf2 modulators in conjunction with traditional neurodegenerative, cardiovascular, or cancer medicines [190].

Despite the current understanding of redox-sensitive transcription factors, signaling crosstalk, and sensor protein switches, several critical questions remain unresolved. For instance, it is still unclear how cells prioritize redox-mediated transcriptional responses when multiple pathways are simultaneously activated, and whether there exists a hierarchical control among NF- $\kappa$ B, Nrf2, HIF-1 $\alpha$ , and AP-1 under

fluctuating redox states [191]. Another open question concerns the threshold at which reversible redox modifications irreversibly shift toward pathological damage, and whether this tipping point can be predicted using dynamic biomarkers. A promising hypothesis is that cells employ context-dependent “redox codes” that integrate intensity, duration, and localization of ROS/RNS signals to orchestrate adaptive versus maladaptive outcomes [192]. Future studies may test whether decoding these redox signatures could enable precision targeting of therapeutic interventions while preserving essential physiological signaling.

**Table 3** Redox signaling-based clinical approaches.

Strategy	Example	Excess	Limitations	Reference
Conventional antioxidants	Vitamin C, Vitamin E, and $\beta$ -carotene	Easily available, safe in moderate doses, and widely effective	Non-specific, potentially disrupts physiological redox signals, and clinical outcomes are inconsistent.	[36]
Specific redox modulator	Nrf2 activators (sulforaphane and bardoxolone methyl)	Increases antioxidant gene expression and endogenous protective effects	Risk of off-target effects and some are still in the clinical trial stage	[183]
Targeted antioxidants	MitoQ and SkQ1	Targeting the main source of ROS (mitochondria) and more selective effects	High cost and still limited to certain indications	[20]
Redox status biomarkers	GSH/GSSG ratio, malondialdehyde, and protein carbonyl	Diagnostic, prognostic, and therapy monitoring tools	Biological variability is high and there is no universal standard.	[185]
Future prospects for redox-based therapy	Precision medicine and combination modulator therapy	Specific to certain redox pathways, can be combined with conventional therapy	Still in the research stage and requires extensive clinical validation	[188]

### Challenges and future research directions

Although the understanding of redox signaling has advanced rapidly in the last two decades, there are still a number of conceptual and technical challenges that need to be overcome to broaden its applications in biology and medicine. The incomplete knowledge of the temporal and geographical dynamics of redox

signaling is one of the primary challenges [193]. ROS and RNS are highly reactive, so their distribution within cells is rapid and heterogeneous [194]. Because of this, it is challenging to pinpoint exactly when and where redox signals are produced, as well as how they are delivered to certain molecular targets [195].

Overcoming these constraints largely depends on the advancement of redox imaging technology and the application of certain biosensors [196]. Biosensors based on oxidation-sensitive fluorescent proteins, like roGFP or HyPer, allow for real-time, direct monitoring of intracellular redox changes [197,198]. This method makes it possible to more precisely map redox variations at the tissue and subcellular levels [199].

Furthermore, a promising avenue for future research is the integration of omics methods, including metabolomics and redox proteomics [200]. Protein residues that experience redox modification can be identified using redox proteomics, while metabolite changes brought on by redox imbalance can be globally analyzed using metabolomics [201,202]. Combining these two methods can yield a thorough understanding of the redox processes implicated in both healthy and diseased states, as well as present chances for the identification of novel therapeutic targets [203].

Additionally, the concept of customized treatment based on each patient's unique redox profile is emerging [204]. Interindividual variations in redox state, which are impacted by environmental, lifestyle, and genetic factors, may serve as a foundation for more targeted therapies [205,206]. This strategy is anticipated to improve the efficacy of treating diseases linked to oxidative stress, reduce side effects, and offer more tailored therapy by leveraging redox biomarker data and omics integration [207].

## Conclusions

Redox signaling represents a fundamental biological mechanism that bridges cellular metabolism with systemic regulation, acting as both a protector of homeostasis and a driver of pathology when dysregulated. The dual nature of reactive oxygen and nitrogen species highlights their context-dependent functions, where controlled fluctuations promote proliferation, immune balance, energy metabolism, angiogenesis, and neurophysiology, while chronic imbalance contributes to cardiovascular disease, neurodegeneration, cancer, metabolic disorders, and aging. This review emphasizes that redox signaling should not be viewed as an isolated cellular process, but rather as a cross-organ communication axis

influencing diverse physiological and pathological outcomes.

From a translational perspective, the limited success of conventional antioxidants underscores the need for pathway-specific modulators, targeted mitochondrial protectants, and biomarker-guided interventions. Future progress depends on refining mechanistic insights through advanced biosensors and omics approaches, ultimately enabling precision redox medicine. By positioning redox balance at the intersection of health and disease, this work provides a framework for novel diagnostic strategies and therapeutic innovations that could reshape approaches to degenerative and chronic conditions.

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## Declaration of Generative AI in Scientific Writing

The authors declare that no generative AI tools were used in the writing or preparation of this manuscript.

## CRedit Author Statement

**Aswin Rafif Khairullah** and **Eny Martindah:** Were responsible for the conceptualization of the review framework and overall study design. **Mohammad Sukmanadi, Sri Mulyati** and **Arif Nur Muhammad Ansori:** Contributed to the development of the methodology and refinement of the research scope. **Bantari Wisynu Kusuma Wardhani** and **Annise Proboningrat:** Conducted the comprehensive

literature search and data curation. **Dea Anita Ariani Kurniasih** and **Ilma Fauziah Ma'ruf**: Performed the formal analysis and interpretation of findings. **Desi Lailatul Hidayah Utomo**, **Riza Zainuddin Ahmad** and **Adeyinka Oye Akintunde**: Prepared the manuscript draft. **Bima Putra Pratama**, **Anggun Khoirun Nikmah**, and **Wita Yulianti**: Were responsible for substantive editing and critical revision of the manuscript. All authors participated in reviewing the final text for intellectual content. **Angel Jelita Brilliant Yuri** and **Imam Mustofa**: Supervised the overall work process. **Herry Agoes Hermadi**: Secured the funding for this study. All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work.

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