ORAL SCI HOMEOST MED

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REVIEW

Redox signaling and homeostasis

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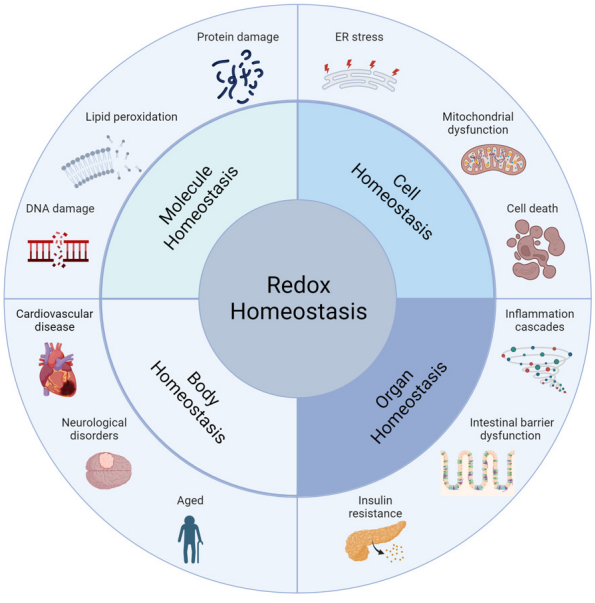
Cite This: *Oral Sci Homeost Med*, **2025**, 1, 9610003 Read Online

ABSTRACT: Homeostasis constitutes a dynamic equilibrium process through which an organism sustains internal stability and adjusts to its external environment. A crucial aspect of this process involves a cascade of redox reactions, generating energy (such as adenosine triphosphate, ATP) and synthesizing essential cellular components (such as nucleic acids) from nutrients to support diverse biological functions. Intracellular redox imbalance, resulting from disruptions in the equilibrium between oxidants and antioxidants, is a hallmark event in numerous pathophysiological processes. This review encapsulates the concept of cellular redox homeostasis, examines the factors and processes contributing to regulatory roles in redox homeostasis, and elucidates how cellular functions can be modulated by targeting these molecular mechanisms. Future advancements will necessitate the development of precise assessment methods for redox homeostasis, the judicious selection of oxidative modulators based on disease characteristics, the rationalization of delivery systems, and the creation of precise interventions. These interventions must consider various factors to achieve optimal modulation either positively or negatively and meet therapeutic goals across different diseases.



KEYWORDS: redox homeostasis, redox signaling, cellular redox regulation, oxidative stress, reductive stress, reactive oxygen species (ROS)

1 Introduction

Homeostasis is an important process that enables biological systems to remain stable and adapt to changing external conditions, thereby facilitating normal activities[1]. As the basic functional unit of an organism, the maintenance of cellular homeostasis plays a key role in ensuring the proper functioning of the organism[2]. The regulation of homeostasis, including ions, lipids, proteins, energy, and redox, as well as other essential factors, is key to preserving cellular functional homeostasis[3]. Redox reactions are the most common chemical reactions in many cellular processes, including deoxyribonucleotide synthesis, protein folding, and cellular respiration (Fig. 1)[4]. During redox reactions, electrons flow from the reducing agent to the oxidizing agent, and the body harbors multiple redox pairs that serve as cofactors or substrates for enzyme- or non-enzyme-neutralizing reactive oxygen species (ROS), maintaining a relatively reductive environment. Redox homeostasis is essential for maintaining physiological responses, and any imbalance in this system can lead to a range of chronic systemic diseases[5,6]. At low levels, ROS function as second messengers, playing a crucial regulatory role in normal cellular activities like cell proliferation, differentiation, and survival[7]. However, excessive accumulation of ROS can target macromolecules such as lipids, proteins, and nucleic acids, disrupting protein function, causing lipid peroxidation, and damaging DNA and RNA. This can contribute to the onset and progression of various diseases, including tumors[8,9]. This review highlights the diversity of molecular regulatory mechanisms governing cellular redox control, with the field of redox signaling continuing to evolve to reveal more

Received: November 27, 2024; **Revised:** February 14, 2025
Accepted: March 4, 2025

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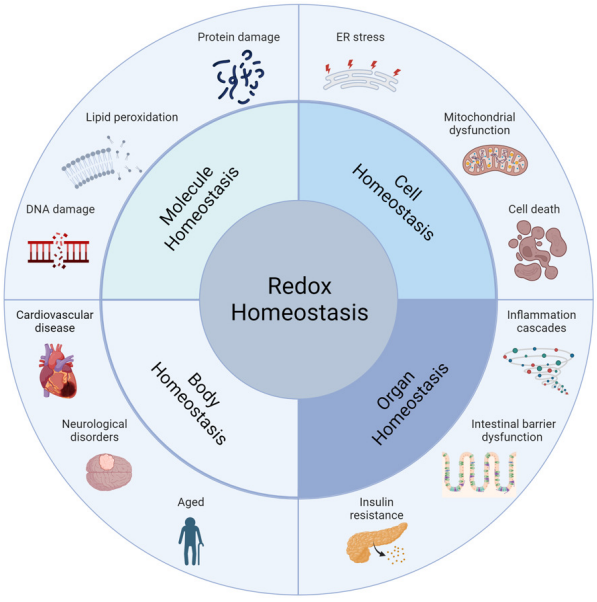

Figure 1 The significance of cellular redox homeostasis. Redox homeostasis is essential for maintaining the normal functioning of molecules, cells, organs, and organisms. Following a disturbance in the homeostatic regulatory system, cells undergo a cascade of functional, structural, and metabolic changes. Consequently, these changes may manifest as abnormal signs, behaviors, and symptoms of disease. Created with BioRender.

interesting and unforeseen targets for redox regulation. In addition, this article delves into the pathophysiology of diseases that arise when cellular redox homeostasis is dysregulated, offering insights for future therapeutic strategies and emphasizing the necessity for in-depth investigation.

2 Concept of cellular redox homeostasis

The concept of cellular redox homeostasis refers to the balanced state of intracellular redox reactions, where electron transfer processes maintain the equilibrium between reducing and oxidizing agents[10]. This balance is critical for sustaining life activities, forming the "golden mean of healthy life" (Fig. 2b)[11]. Redox homeostasis ensures that biochemical reactions involved in energy metabolism, hormone synthesis, and other vital processes function efficiently and adaptively within the cell[12].

At the core of cellular redox reactions lies electron transfer, a fundamental biochemical process that predominantly occurs in the mitochondria[13]. Here, electrons reduce oxygen in a tightly regulated sequence, releasing energy that drives ATP synthesis, the primary energy currency of the cell[13]. Beyond energy metabolism, the redox state directly influences protein function. For instance, oxidation of sulfhydryl groups in protein residues, such as cysteine, can induce conformational changes, impacting their activity and structural integrity[14]. A notable example is glyceraldehyde 3-phosphate dehydrogenase (GAPDH), which shifts from a glycolytic enzyme to a nuclear DNA repair participant upon oxidation[15]. This oxidative modification can result in alterations in protein activities, exerting a decisive influence on cell fate.

Redox homeostasis also plays an integral role in regulating cellular signaling pathways. Oxidative modifications act as molecular switches, modulating the activity of key signaling proteins. For example, cytokines and growth factors can activate oxidoreductases, triggering downstream signaling cascades[16]. A classic case is the NF-κB pathway: under oxidative conditions, the inhibitory protein IκB undergoes phosphorylation and degradation, enabling NF-κB p65 to translocate to the nucleus and regulate inflammation-associated gene expression[17]. These mechanisms link redox dynamics to cellular processes such as proliferation, differentiation, and apoptosis.

Furthermore, the adaptive capacity of the redox network is critical for cellular responses to environmental and internal stressors. Impairment of this adaptive system can lead to cellular damage and disease[18]. When the cell is stimulated by internal and external oxidative damage, the NRF2 system will be activated, enabling the cell to promote gene expression of a variety of antioxidant enzymes/synthases through this system, thus realizing a reserve against oxidative stress damage and improving damage tolerance or robustness[19].

Given the critical role of redox homeostasis in various cellular

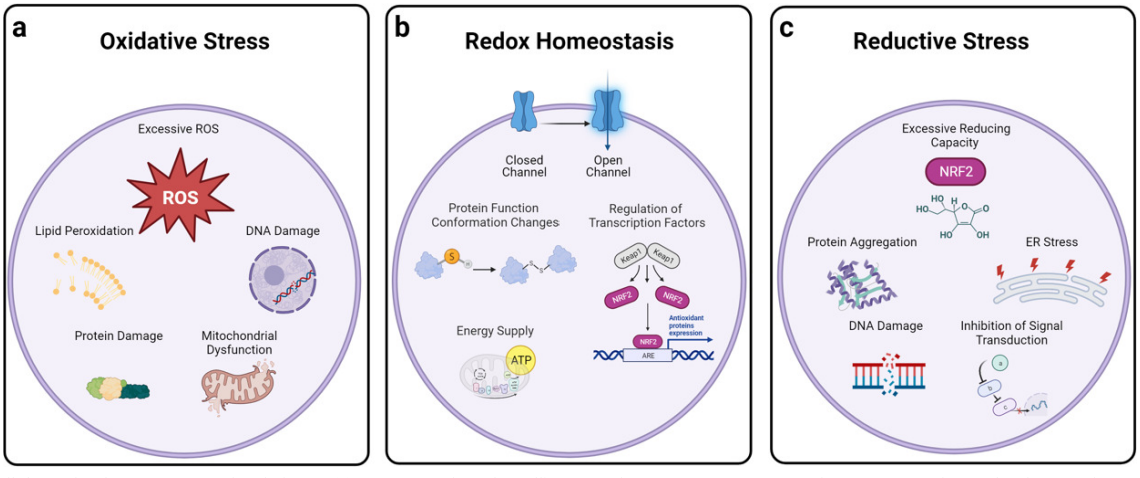

Figure 2 Cellular redox homeostasis and imbalance. (a) ROS exceeding the cell's antioxidant capacity triggers oxidative stress, inducing lipid peroxidation, protein and DNA damage, and mitochondrial impairment. (b) Intracellular redox homeostasis can tune the opening and closing of ion channels, metamorphose the conformation and functionality of proteins, manage the operation of transcription factors, and generate ATP. (c) When the cellular reducing capacity is excessive, such as hyperactivation of NRF2 or exorbitant reducing agents, reductive stress emerges. Reductive stress can culminate in anomalous protein aggregation, endoplasmic reticulum stress, DNA damage, and the suppression of signal transduction. Created with BioRender.

biological processes, an imbalance between oxidation and antioxidants can disrupt cellular and organismal homeostasis. When the equilibrium between cellular oxidation and reduction is disturbed, leaning toward oxidation, oxidative stress (OS) occurs. Conversely, when it leans toward reduction, it is characterized as reductive stress (RS), akin to an antioxidant overdose[20]. Among them, OS is mainly due to ROS exceeding the antioxidant capacity of cells, and excessive ROS can cause irreversible damage to cellular composition and function (Fig. 2a)[21]. ROS directly or indirectly damage DNA, proteins, and lipids, leading to alterations in cellular chemistry, destruction of cell membranes, and blockage of key cellular enzymes and energy production, which in turn can lead to a wide range of pathologies such as aging, cancer, neurodegenerative diseases, cardiovascular diseases, and diabetes[22]. RS is mainly caused by an excessive reducing capacity within the organism, such as silencing of endogenous Keap1 and overexpression of NRF2, or excessive amounts of substances with high reduction potential, such as cysteine, vitamin C, and vitamin E[23]. Its principal effects encompass cellular protein aggregation, DNA damage, mitochondrial dysfunction, endoplasmic reticulum (ER) stress, inhibition of growth factor-mediated signaling, impairment of cellular metabolism, function, differentiation, and ultimately cell death (Fig. 2c)[24].

Therefore, cellular redox homeostasis provides a stable microenvironment conducive to the normal functioning of biomolecules and is essential for typical physiological cellular functions. The perspectives of OS and RS expand our understanding of cellular redox homeostasis and explain why relying solely on antioxidants may not accomplish the desired effect of maintaining redox homeostasis. An in-depth understanding of the molecular regulatory mechanisms of redox homeostasis and its pathogenic implications is necessary to identify specific and safe therapeutic targets for treating diseases associated with cellular redox imbalance.

3 Mechanisms of redox homeostatic regulation in cells

Maintenance of redox homeostasis is critical for normal cellular function and survival. The following section discusses the roles of the two major antioxidant systems (Thioredoxin, Trx and Glutathione, GSH), redox-sensitive transcription factors, and additional enzymes or non-enzymatic systems in mediating cellular redox homeostasis and disease (Fig. 3). Exploring the mechanisms of cellular redox homeostasis will contribute to a deeper understanding of the nature of cellular biological activities and disease development, providing new ideas and approaches for disease treatment.

3.1 Thioredoxin (Trx) system

The Thioredoxin (Trx) system is an important antioxidant reduction system in the body that is closely related to cell

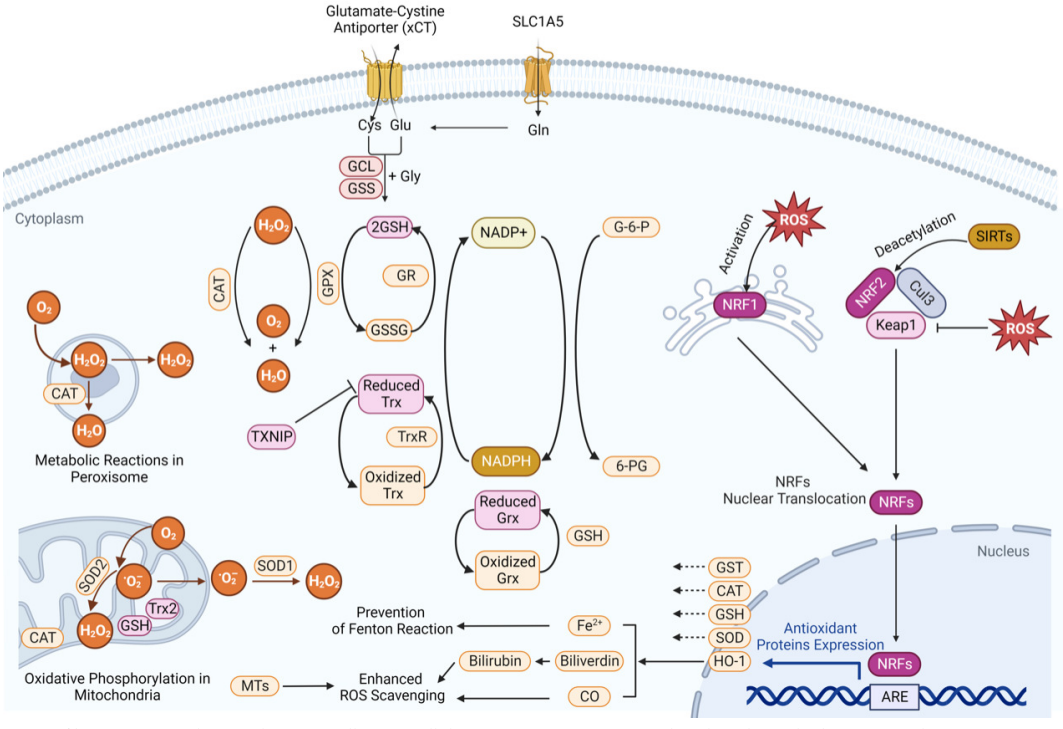

Figure 3 Mechanisms of homeostatic redox regulation in cells. Intracellular ROS encompasses mitochondria, the endoplasmic reticulum, peroxisomes, etc. NRFs can be activated and translocated into the nucleus, initiating an antioxidative response to ROS through the activation of antioxidant response elements. During neutralization and repair of ROS/oxidized proteins, Trx, Grx, etc. either utilize GSH as a substrate or oxidize themselves. They then are reduced via accepting electrons from NADPH, establishing an antioxidant cycle. NADPH can be generated from $NADP^+$ receiving electrons from PPP. Abbreviation: Cys = cysteine, Glu = Glutamic acid, Gln = Glutamine, GCL = glutamate-cysteine ligase, GSS = glutathione synthetase, GSH = glutathione, GR = glutathione reductase, CAT = catalase, GPX = glutathione peroxidase, Grx = glutaredoxin; ROS = reactive oxygen species, SOD = superoxide dismutases, TrxR = thioredoxin reductases, Trx = thioredoxin; NADPH= nicotinamide adenine dinucleotide phosphate; 6-PG = 6-phosphogluconate, G-6-P = glucose-6-phosphate, PPP = pentose phosphate pathway. Created with BioRender.

proliferation, differentiation, and death. It has been implicated in various diseases, such as tumors, neurodegenerative disorders, rheumatoid arthritis, hypertension, and myocarditis[25]. The Trx system consists of Trx, thioredoxin reductase (TrxR), and nicotinamide adenine dinucleotide phosphate (NADPH)[25] (Fig. 4). Among them, Trx has a dual antioxidant role, directly neutralizing reactive ROS and repairing oxidized proteins[26]. Trx is mainly involved in redox reactions as a hydrogen donor through the reversible oxidation of its active center, dithiol, to disulfide, accompanied by the transfer of two electrons and two protons[27]. TrxR is the only known enzyme that can reduce Trx in the oxidized state, transferring electrons from NADPH to its disulfide bonding active site, and then to oxidized Trx[28]. Thus, the system operates through a disulfide exchange reaction in which Trx reduces oxidizing substances. TrxR acts synergistically with NADPH to reduce Trx, thereby catalyzing a series of physiological and biochemical reactions in organisms, and participating in numerous cellular physiological processes.

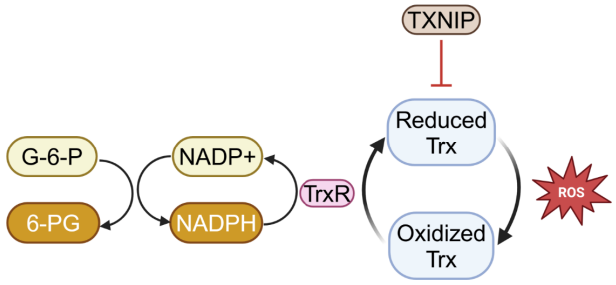

Figure 4 Mechanisms of homeostatic redox regulation by Thioredoxin (Trx) system. Trx directly neutralizes (ROS or repairs proteins that have been damaged oxidatively, while undergoing a transformation from a reduced state to an oxidized state. TrxR reduces oxidized Trx with the assistance of electrons derived from NADPH, and Trx is inhibited by TXNIP in the cytoplasm. Created with BioRender.

Aerobic glycolysis is a hallmark of cancer. It is a metabolic preference that allows cancer cells to biosynthesize via glycolysis, even under normoxic conditions to sustain rapid proliferation[29]. Trx1 regulates the activity of glucose-6-phosphate dehydrogenase (G6PD), the first key enzyme of the pentose phosphate pathway (PPP), via interaction with G6PD. This interaction enhances the oxidative flow within the PPP, leading to increased production of NADPH. The elevated NAPDH levels facilitate the scavenging of ROS, effectively counteracting OS[30]. Therefore, maintaining adequate levels of NADPH in Trx1 is critical for the survival of cancer cells in OS[31]. In addition, intranuclear Trx1 is more resistant to oxidation than cytoplasmic Trx1, which is more likely to lead to the resistance of tumor cells to chemotherapeutic agents[32]. Studies have shown that IL-6-stimulated Trx1 nuclear translocation promotes epithelial-mesenchymal transformation and invasive metastasis of colorectal cancer cells by enhancing the IL-6/STAT3 signaling pathway through interactions with STAT3, thus providing a new theoretical basis for identifying Trx1 nuclear translocation as an effective therapeutic target for colorectal cancer[33]. In neurodegenerative diseases, Trx-interacting protein (TXNIP), an inhibitory protein of Trx, is usually elevated, and the inhibition of Trx activity leads to increased cellular susceptibility to OS injury, which in turn leads to disease progression[34]. It was found that upregulation of TXNIP expression enhances ROS-induced injury and Aβ aggregation, activates microglia through the NLRP3/caspase-1/IL-1β pathway, and is associated with seeding spreading of Aβ-associated tau proteins in Alzheimer's disease patients[35].

Furthermore, in an inflammatory environment, Trx1 upregulation can place cytoprotective sulfhydryl residues on the cell membrane in a reduced state, thus playing a role in NK cell survival[36]. Although this phenomenon may protect cells from hydrogen peroxide-mediated NK cell dysfunction, the level of protection is limited as chronic nitrosative OS may lead to NK cell hypofunction and loss of cytotoxic activity[37]. In periodontal ligament stem cells, knockdown of Trx1 leads to increased ROS and disruption of Wnt/β-catenin signaling, thereby inhibiting osteogenic differentiation. This finding highlights the critical protective role of Trx1 in periodontitis and suggests that it is a potential therapeutic target for refractory periodontitis associated with OS[38]. In vascular endothelial cells, Trx overexpression minimizes the oxidative modification of redox-active proteins (such as eNOS) and maintains them in a functional state, which could prevent age-related hypertension[39]. Meanwhile, it has been demonstrated that Cys1483 oxidative specificity of mTOR mediates the downregulation of endogenous Trx1 and induces mitochondrial dysfunction in cardiomyocytes[40]. Thus, Trx1 performs a vital pumping function and maintains redox homeostasis at baseline in the adult heart, exhibiting antihypertensive effects. Additionally, endogenous Trx1 emerges as a significant mediator of metabolic gene expression.

Intervention of the Trx system based on cellular redox homeostasis is an important target for drug therapy in many diseases. However, the specific molecular mechanism by which the Trx system eliminates ROS and prevents disease has not been fully elucidated, and many unknown molecules and sites regulated by the Trx system in organisms require further study. Future research on the Trx system should continue to investigate the specific mechanism of the molecular system in eliminating OS, such as ROS, as well as the balancing and coordinating role of the molecular system among redox systems in the cell. In addition, research should focus on the function and application of the Trx system in disease prevention and treatment as well as the search for relevant molecular targets and drug screening. In conclusion, the study of the Trx system offers a crucial perspective for understanding the survival mechanisms of organisms inhabiting extreme conditions, such as OS.

3.2 The Glutathione (GSH) system

The Glutathione (GSH) system, which is mainly composed of GSH and related enzymes, is another key cellular redox regulatory system that plays an important role in maintaining normal cellular metabolism, scavenging free radicals, and protecting cells from oxidative damage (Fig. 5)[41]. GSH is a tripeptide comprising glutamic acid, cysteine, and glycine combined with sulfhydryl groups. GSH is available in both reduced (GSH) and oxidized (GSSG) forms, with reduced GSH accounting for the majority of GSH under physiological conditions[42]. Related enzymes in the GSH system include glutathione peroxidase (GPX), glutathione reductase (GR), glutaredoxin (Grx), and glutathione S-transferase (GST). GPX is an important peroxidative catabolic enzyme that is widely present in organisms, with selenocysteine as the active center. It can catalyze the conversion of GSH to GSSG, reduce toxic peroxides to non-toxic hydroxyl compounds, and simultaneously promote the decomposition of H_2O_2, thus protecting the structure

and function of cell membranes from the interference and damage caused by peroxides[43]. GR catalyzes the conversion of GSSG to GSH while oxidizing nicotinamide adenine dinucleotide phosphate (NADPH) to $NADP^+$[44]. It not only plays a key role in the OS response for ROS scavenging but also participates in the ascorbate-glutathione cycle, thereby maintaining adequate intracellular levels of reduced GSH[45]. Additionally, Grx and GST are involved in ROS degradation when GSH is used as a substrate. Grx serves as an integral component of the thioredoxin superfamily, functioning as a sulfhydryl transferase, encouraging the exchange of sulfhydryl-disulfide bonds or diminishing the protein glutathione disulfide to ensure redox equilibrium within cells[46]. Similar to GPX, GST catalyzes the binding of the electrophilic groups of certain endogenous or exogenous harmful substances to the sulfhydryl groups of reduced GSH to form more soluble, non-toxic derivatives that protect cells from OS[47]. These enzymes and proteins play important roles in the synthesis, reduction, transfer, and oxidation of GSH, maintaining GSH and cellular redox homeostasis to protect the body from damage.

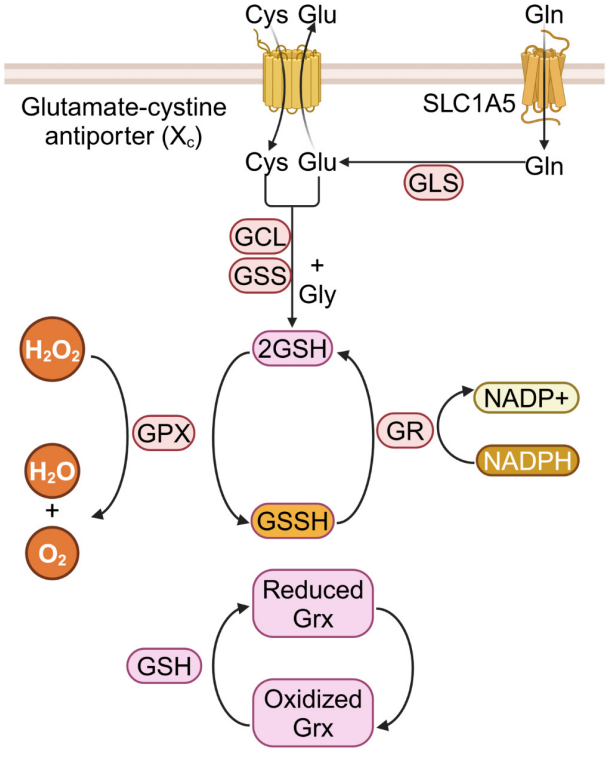

Figure 5 Mechanisms of homeostatic redox regulation by Glutathione (GSH) system. Through the System Xc−, cysteine (Cys) and glutamic acid (Glu) work together to synthesize glutathione (GSH) via the actions of glutamate cysteine ligase (GCL) and glutathione synthetase (GSS). GSH can directly reduce oxidized glutaredoxin (Grx) or act as a substrate for glutathione peroxidase (GPX) to neutralize reactive oxygen species (ROS), resulting in its conversion to oxidized glutathione (GSSG). Moreover, glutathione reductase (GR) employs electrons derived from NADPH to regenerate GSH from GSSG. Created with BioRender.

In immune cells, GSH levels and the overall activity of the GSH system influence macrophage function and polarization patterns[48]. Increased GSH oxidation impairs phagocytosis and macrophage survival. In addition, Grx expression and enzyme activity were significantly reduced in the lung tissues of mice with acute lung injury, and the absence of Grx and increased levels of glutathionylation of proteins in macrophages significantly alleviated acute lung injury. This suggests that glutathionylation of proteins in macrophages plays an important role in the disease progression of acute lung injury, providing a novel insight into the targeted treatment of lung injury using redox strategies[49]. GSH levels regulate dendritic cell differentiation and function as antigen-presenting cells[50]. GSH levels in dendritic cells can also determine T-cell polarization patterns by affecting IL-27 and IL-12 production, and GSH depletion is associated with the differentiation of naïve T-cells, thereby inhibiting dendritic cell maturation and inflammatory cytokine production, leading to severe cellular dysfunction[51]. In addition, the deletion of GPX4 in T cells selectively abrogated immune mouse follicular helper T (TFH) cells and germinal center responses. Enhanced GPX4 expression in T cells enhances TFH function and improves protective humoral immunity after infection and vaccination[52]. Expression of the GSH system is often elevated in cancer cells because they can withstand a more oxidizing environment than normal cells[53]. In a variety of RIPK3-negative cancer cells, GPX is associated with H_2O_2-induced apoptosis. The deletion of GPX significantly increases cellular H_2O_2 levels, leading to apoptosis through the sustained activation of JNK and caspase-8 expression[54]. In addition, GST is overexpressed in numerous cancers and is associated with tumorigenesis and reduced survival. Inhibition of GST inhibits AKT/GSK-3β pathway signaling and promotes cancer cell apoptosis by regulating mitochondrial apoptotic pathway-related proteins, directly leading to mitochondrial dysfunction[55]. However, the opposite can also occur. GPX3 reduces glucose uptake, extracellular lactate content, and the rate of extracellular acidification in multiple myeloma cells by decreasing ROS levels and increasing the rate of cellular oxygen consumption, thereby inhibiting multiple myeloma cell viability and malignant melanoma progression[56]. Besides, various Grxs can protect lens epithelial cells from OS-induced epithelial-mesenchymal transition via the inhibition of casein kinase and integrin-linked kinase[57]. Meanwhile, in human endothelial cells, decreased levels of GPX1 induce pro-inflammatory regulation, as evidenced by the enhancement of the adhesion molecules ICAM1 and VCAM1[58]. However, elevated GPX1 levels attenuate the H_2O_2-induced vasodilatory response because oxidative changes in cystine residues amplify the hyperpolarization of potassium channels in vascular smooth muscle cells[59]. Thus, moderate GPX1 levels protect the endothelial vasodilatory response by inhibiting the deleterious effects of excess ROS and preserving physiologically active NO.

Despite our understanding of the GSH system, there are still many unanswered questions regarding its biochemical mechanisms. Future research directions involve both basic and applied aspects. In the aspect of basic research, the interactions of the GSH system with other biomolecules and their effects on cellular redox homeostasis need to be further elucidated. Many proteins are believed to be redox regulated through the GSH system; however, only a small fraction have been identified as targets of this system. Concerning applied research, drug targets of the GSH system should be further explored to conduct studies on the clinical application of the GSH system and further explore the value of its application in the diagnosis and treatment of diseases. In addition, new techniques for visualizing redox signals *in vivo* should be developed to study the response of the GSH system to environmental stress and its role in the aging process, which is of great significance for understanding the adaptability and tolerance of organisms to their environment.

3.3 NRF transcription factors

In addition to the aforementioned antioxidant systems, NRF, a pivotal transcription factor that regulates cellular resistance to oxidative stress (OS), plays a crucial role in modulating the expression of various intracellular antioxidant enzymes[60]. NRF1 and NRF2, members of the Cap 'n' Collar basic-region leucine zipper (CNC-bZIP) family, engage in a reciprocal regulatory relationship, effectively integrating multi-level signals and fine-tuning gene expression networks (Fig. 6). This interplay is essential for maintaining cellular and mitochondrial redox balance as well as energy metabolism homeostasis[61]. Notably, Cys342 and Cys640 in NRF1 represent redox-sensing sites located within its N-glycodomain and DNA-binding domain, respectively[62]. NRF1 serves as a composite topological regulatory molecule that acts as a sensor, transducer, and effector, capable of detecting changes in glycolipid, cholesterol, and redox states both intracellularly and extracellularly, subsequently transducing these signals to elicit appropriate cellular responses[63]. Furthermore, NRF1 regulates the transcriptional expression of proteasome subunit genes, facilitating the removal of oxidative damage from misfolded proteins and thereby sustaining intracellular protein homeostasis[64].

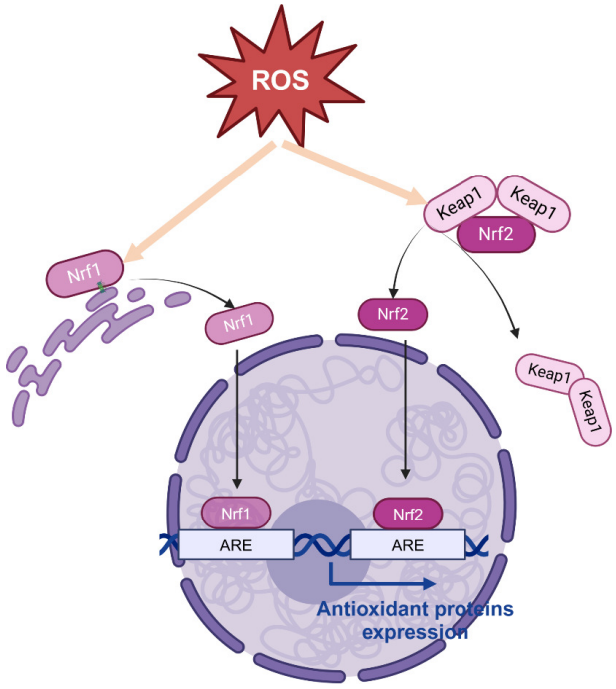

Figure 6 Mechanisms of NRFs in regulating redox homeostatic. ROS can stimulate the release of NRF1 from the endoplasmic reticulum and NRF2 from the inactive Nrf2-KEAP1 complex in the cytoplasm. This process subsequently leads to the translocation of NRFs to the nucleus, where they activate antioxidant response element (ARE)-dependent genes. Created with BioRender.

In response to OS, the active cysteine residue on Keap1—a pivotal sensor of oxidative stress—undergoes modification, leading to the dissociation of NRF2 from Keap1. This process allows NRF2 to translocate from the cytoplasm to the nucleus[65], where it binds to the antioxidant response element (ARE) to promote the transcription of a cohort of antioxidant genes[66]. NRF2 plays a multifaceted role in overseeing the biosynthesis, utilization, and regeneration of critical antioxidant molecules such as glutathione (GSH), thioredoxin (Trx), and NADPH. Additionally, it regulates reactive oxygen species (ROS) production from mitochondria and NADPH oxidase, influences mitochondrial membrane potential, fatty acid oxidation, and substrate utilization for aerobic respiration, ultimately impacting ATP synthesis[67].

The NRF1/HO-1 axis has been shown to mitigate the cytotoxic effects of cisplatin in hepatocytes and HEK293 cells by enhancing PINK1/Parkin-mediated mitophagy and inhibiting the MAPK signaling cascade, thus providing insights into potential protective measures against cisplatin toxicity[68,69]. Similarly, the NRF2/HO-1 signaling pathway facilitates mitophagy and prevents apoptosis in chondrocytes and BV2 cells, contributing to the alleviation of intervertebral disc degeneration and neuronal damage[70]. In the context of hypoxia-induced stress, NRF1 significantly reduces ROS generation in cardiomyocytes, which is crucial in preventing cardiomyocyte apoptosis, a critical factor in heart failure[71]. Collaborating with PGC-1α, NRF2 further protects cardiomyocytes from OS by enhancing mitochondrial biogenesis during septic cardiac insult[72]. Moreover, NRF1 initiates a Selenoprotein T (SELENOT)-centered antioxidant cascade, enabling PC12 cells to adapt to metabolic fluctuations and progress through neuroendocrine maturation[73]. By degrading ROS, NRF2 also protects mouse embryonic fibroblasts from lipotoxicity, presenting a novel therapeutic strategy for non-alcoholic fatty liver disease[74]. In hepatic cancer cells, NRF1 enhances the expression of collectrin (CLTRN), promoting cellular radiosensitivity via the GSH metabolic ferroptosis pathway[75]. Furthermore, inhibiting NRF2 activity results in decreased expression levels of GPX4, HERC2, and VAMP8, which heightens ROS generation and leads to the accumulation of low-ferritin proteins in autophagosomes, thereby facilitating ferroptosis in cancer cells[76].

Additionally, crosstalk between NRF1 and NRF2 has been observed in H9C2 cells. Specifically, NRF1 overexpression boosts NRF2 expression and enhances mitochondrial function, providing resistance against CoCl2-induced OS[77]. Conversely, silencing NRF1 in bone marrow-derived stem cells (BMSCs) compromises NRF2-mediated antioxidant defenses and elevates mitochondrial ROS levels, ultimately leading to apoptosis[78]. In HepG2 cells, depletion of NRF1 results in a dramatic increase in ROS levels that cannot be mitigated by excessive NRF2 elevation[79]. These findings suggest that NRF1 is a critical transcription factor involved in redox regulation, it may play a more significant role than NRF2. Furthermore, the activation of NRF1 may largely depend on pathways that are independent of ROS. However, the interaction between NRF1 and NRF2 warrants further investigation.

While the crucial roles of NRFs in physiological processes have been established, their complete transcriptional landscape and the interplay between NRFs and various other regulatory factors remain inadequately understood. Identifying co-regulators, co-repressors, and binding cohorts associated with NRFs is essential for elucidating this complex gene regulatory network. Moreover, a significant unresolved question pertains to the correlations among different NRFs and their interactions with other factors. Specifically, how is the balance among redox reactions, endoplasmic reticulum stress, and protein homeostasis maintained in NRFs during stress conditions? Future research should prioritize an in-depth examination of the molecular regulatory mechanisms underlying NRF activation and the expression of their downstream antioxidant target genes. Such investigations are expected to yield novel insights into antioxidant therapies and provide valuable references for the prevention and treatment of a diverse array of diseases.

3.4 Other enzymes

In addition to the aforementioned enzymes for the two major antioxidant systems, numerous other enzymes play key roles in maintaining cellular redox homeostasis.

3.4.1 SOD

Superoxide dismutase (SOD) stands as the first line of defense against ROS, converting superoxide anion radicals into H_2O_2[80]. Subsequently, enzymes such as CAT and GPX[81]. The catalytic effect of SOD is achieved through the cyclic oxidation and reduction of metal ions by gaining and losing electrons[82]. In breast cancer cells, SOD knockdown leads to the accumulation of ROS, reducing ERK1/2 activity, thereby inhibiting cell proliferation and migration[83]. Meanwhile, inhibition of SOD not only significantly increased the chemosensitivity of esophageal cancer cells to cisplatin[84], but also prevented H_2O_2-induced metastasis of pancreatic cancer cells via blocking the PI3K/Akt/NF-κB signaling pathway, which brought unprecedented prospects for cancer treatment[85]. In addition, SOD can inhibit the activation of signaling pathways by regulating the production of ROS, thus hindering the differentiation of T cells, which may lead to a promising therapeutic option for the treatment of T-cell-mediated diseases[86]. SOD can also regulate the phosphorylation of Smad3 to remove ROS, thus promoting the osteogenic differentiation of periodontal ligament stem cells, laying a theoretical foundation for the treatment of alveolar bone regeneration[87].

3.4.2 CAT

Catalase (CAT) is an iron-porphyrin cofactor-bound enzyme that catalyzes the breakdown of hydrogen peroxide into oxygen and water and is mainly found in the peroxisomes of cells[88]. The catalytic process involved the breakdown of two hydrogen peroxide molecules into one oxygen molecule and two water molecules through a two-step reaction[89]. In addition, CAT can be used to detect redox states within cells. When a cell is in a state of OS, CAT activity is increased in response to excess free radicals[90]. Therefore, by detecting CAT activity, it is possible to understand the redox state within the cell and assess its health[91]. CAT-deficient mouse embryonic fibroblasts exhibit a severe senescence phenotype due to the overproduction of ROS at an early stage, which can be inhibited by increasing CAT activity[92]. Reduced CAT activity is associated with increased oxidative stress, which contributes to aging and a range of human diseases, particularly neurodegenerative disorders like Alzheimer's and Parkinson's diseases[93]. For instance, a deficiency in catalase can exacerbate metabolic syndrome and result in neurological and other related conditions[94]. Therefore, CAT has the therapeutic potential to act as an inhibitor of ROS to restore a healthy lifespan. In addition, CAT overexpression can ameliorate cardiac dysfunction by modulating OS-mediated autophagy, iron metabolism, and mitochondrial damage in cardiomyocytes[95]. Conversely, an increase in the levels of CAT protein enables cervical cancer cells to withstand stronger OS[96], yet inhibition of CAT activity in prostate cancer cells triggers cellular autophagy, catabolism of major iron storage proteins, and ferro-metamorphic responses, suggesting that CAT may be a promising new target for the development of therapeutic treatments in prostate cancer[97].

3.4.3 HO-1

Heme oxygenase 1 (HO-1) is an important antioxidant enzyme that catalyzes heme to ferrous iron, carbon monoxide, and biliverdin[98]. Degradation of the heme moiety is conducive to preventing its pro-oxidant effect[99]. In contrast, the byproduct biliverdin and its reduced form bilirubin have potent ROS scavenging activity against peroxide, peroxynitrite, hydroxyl, and superoxide radicals[100]. In mice, reduced expression and enzyme activity of HO-1 lead to slower healing of skin wounds, and HO-1 deficiency is associated with the development of diabetic kidney disease[101]. Additionally, studies show that HO-1 levels are decreased in patients with peripheral artery disease[102]. In vascular smooth muscle cells and cardiomyocytes, upregulation of HO-1 inhibited ROS production[103]. HO-1 is upregulated in various pathological conditions. Drugs that specifically inhibit HO-1 can disrupt intracellular redox homeostasis in non-small lung cancer cells, ultimately leading to cell death, suggesting a high therapeutic potential of HO-1 in maintaining cellular redox homeostasis[104]. However, upregulation of HO-1 in cells may induce OS triggered by large amounts of unutilized iron, leading to iron mutations characterized by lipid peroxidation and iron accumulation[105], which in turn lead to mitochondrial miniaturization and increased ROS generation[106].

3.5 Other non-enzymes

In addition to the above-mentioned antioxidant enzymes, there are various non-enzymatic antioxidants, including proteins and small molecules.

Metallothioneins (MTs) are a well-known family of low-abundance cytoplasmic proteins that play a crucial role in reducing prooxidant levels via two main mechanisms[107]. First, MTs bind to and stabilize metal ions, thereby reducing the production of harmful free radicals. Second, MTs have a high cysteine content that neutralizes free radicals[108]. In colorectal cancer cells, overexpression of MTs can inhibit cell proliferation and migration[109]. In C2C12 cells, a lack of MT stimulates the expression of slow-twitch myosin rather than promoting the formation of rapid-twitch myotubes[110]. In addition, MT overexpression enhances osteoblast differentiation with potentially antioxidant effects[111]. Similarly, S-sulfhydrate MT has a potent protective activity against oxidative damage induced by heavy metal exposure[112].

In addition to the aforementioned cytoplasmic proteins, transmembrane transport proteins play important roles in maintaining cellular redox homeostasis. The cystine transporter solute carrier family 7 member 11 (SLC7A11, also known as xCT) is an indispensable amino acid transporter responsible for the import of extracellular cystine, which is used for the synthesis of GSH during antioxidant processes[113]. Based on its cystine transport function, SLC7A11 is indirectly involved in ROS detoxification and is highly expressed in various tumors[114]. Therefore, the downregulation of SLC7A11 enhanced cell sensitivity to OS. Inhibition of SLC7A11 in human glioma[115] and lung cancer cells[116] results in decreased GSH levels, which in turn causes iron toxicity characterized by lipid peroxidation. However, in SLC7A11-overexpressing cancer cells, large amounts of NADPH are consumed by the reduction of cystine to cysteine, which can lead to depletion of intracellular NADPH and triggers disulfide stress and cell death[117].

Finally, many non-proteins and small-molecule antioxidants within the cell are powerful antioxidants, including carotenoids,

vitamin C (ascorbic acid), vitamin D derivatives, flavonoids, N-acetyl cysteine (NAC), and α-tocopherol[118]. Vitamin C is a safe, natural, and common functional antioxidant with relatively stable effects[11]. It provides two H^+ ions during the conversion of vitamin C to dehydrovitamin C, which directly scavenges free radicals and reduces oxidized GSH[119]. Vitamin C also exhibits indirect antioxidant effects by reducing oxidized vitamin E and sulfhydryl groups to their reduced forms[119]. However, it has also been found that large amounts of vitamin C accumulate hydrogen peroxide by depleting intracellular antioxidants, which induces ROS generation and exerts antitumor effects[120]. Studies on chorionic cells have also shown that high doses of vitamin C exacerbate the increase in mitochondrial ROS[120]. Physiological doses of vitamin C do not exhibit a significant inhibitory effect on tumors and may even promote tumor growth. In contrast, high doses of vitamin C are clinically recognized to induce oxidative stress by depleting antioxidants[121]. Therefore, vitamin C is recommended for anti-tumor treatment, requiring blood concentrations exceed 1 mol/L[122]. Therefore, although vitamin C is an essential nutrient with significant antioxidant properties, its potential pro-oxidative effects must be recognized, and appropriate levels of vitamin C intake must be carefully considered. Characterized by the methylation of the chromanol ring, vitamin E can be divided into eight derivative forms[123]. Among these forms, α-Tocopherol (α-TOH) is known to be the most active antioxidant[124]. The antioxidant protection provided by α-TOH is attributed to its ability to scavenge free radicals generated from lipid biomolecules, thereby interrupting the free radical chain reaction and reducing lipid peroxidation. Studies have also shown that α-TOH may hold promise as an adjuvant for compensating for ischemic and re-perfused injury, atherosclerosis, arthritis, and other conditions[125]. Vitamin E, specifically α-tocopherol, is a crucial antioxidant in the skin and is regarded as one of the most effective compounds in dermatologic formulations for addressing skin aging[126]. It is widely utilized in clinical practice to help delay the signs of skin aging. Furthermore, vitamin E's antioxidant properties can enhance sperm motility, making it a recommended nutritional supplement for individuals preparing for pregnancy[127]. Coenzyme Q10 (CoQ10) is a physiological component of the human mitochondrial electron transport chain. Its half-reduced and fully reduced forms allow CoQ10 to function as an antioxidant[128]. CoQ10 is the only lipid-soluble antioxidant that is synthesized within the body[129]. It can also be obtained from the diet, primarily from meat, poultry, fish, and to a lesser extent, fruits and vegetables. While endogenous synthesis was previously believed to be the main source under normal physiological conditions, the ability to synthesize CoQ10 decreases with age, which may not meet the needs of healthy adults. In addition to its antioxidant capacity, CoQ10 can also enhance cellular metabolism, and it is therefore clinically utilized as an adjuvant treatment for myocarditis and liver cancer[130].

4 Conclusion and prospects

Redox homeostasis operates as a dynamic linchpin in cellular physiology, integrating metabolic activity, signaling cascades, and stress adaptation through sophisticated crosstalk between the Trx and GSH systems, redox-sensitive transcription factors, and enzymatic/non-enzymatic antioxidants. This regulatory network transcends conventional antioxidant defense mechanisms, functioning instead as a cellular "operating system" that dynamically calibrates redox potentials across subcellular compartments. Despite advances in mapping redox components, critical gaps persist in modeling the temporal dynamics of redox fluctuations, translating mechanistic insights into clinically actionable strategies, and developing sustained modulation technologies capable of preserving redox balance without disrupting physiological signaling.

The emerging recognition of cellular redox individuality aligns with the paradigm of precision medicine, suggesting a transformative approach to disease classification. Traditional phenotypic categorization could be augmented by redox-defined stratification, where disorders such as neurodegenerative diseases or metabolic syndromes are subclassified based on distinct redox signatures. For instance, Parkinson's disease variants characterized by glutathione depletion or diabetic subgroups with thioredoxin dysregulation might respond differentially to tailored antioxidant therapies. Realizing this vision requires a paradigm shift from static biomarker measurements to dynamic profiling methodologies. Continuous redox sensors, temporal multi-omics platforms, and advanced imaging modalities with spatiotemporal resolution could capture the oscillatory nature of redox signaling, moving beyond single-timepoint snapshots to map disease trajectories and therapeutic windows.

Therapeutic innovation faces three interconnected challenges: achieving precision targeting of redox lesions, adapting interventions to microenvironmental context, and resolving the Janus-faced roles of reactive species as both signaling messengers and cytotoxic agents. Nanotechnology-driven solutions, such as stimuli-responsive carriers for organelle-specific antioxidant delivery, hold promise for mitochondrial or nuclear redox modulation. Concurrently, redox "theranostics" capable of sensing local oxidative states and adjusting therapeutic activity in real time could overcome the spatial indiscrimination of current antioxidants. These advancements must be coupled with computational frameworks integrating multi-scale redox data, from molecular oscillations to systemic homeostasis, to predict and manage paradoxical effects of interventions.

The clinical application of antioxidants remains fraught with challenges rooted in temporal, spatial, and individual variability. Bulk antioxidant administration often disrupts physiological redox rhythms, while poor tissue specificity risks off-target effects. The biphasic nature of redox modulation—where supra-physiological doses may paradoxically exacerbate oxidative damage—demands chronotherapeutic approaches synchronized with endogenous redox cycles. Individual genetic and epigenetic variability further complicates treatment standardization, necessitating personalized dosing strategies informed by redox phenotyping.

Future progress hinges on synergistic development of enabling technologies: real-time redox diagnostic platforms for point-of-care monitoring, closed-loop delivery systems that dynamically adjust antioxidant release, and patient-specific digital twins simulating redox network responses. By transcending the antiquated dichotomy of "oxidants as villains" and "antioxidants as saviors," next-generation redox medicine may pioneer "reset therapies" that restore homeostatic set points in chronic diseases while preserving vital signaling functions. This paradigm shift from global antioxidant supplementation to precision redox reprogramming could redefine therapeutic strategies across neurodegeneration, metabolic disorders, and cancer, ultimately bridging the chasm between mechanistic understanding and clinical translation.

Acknowledgements

This study was supported by the National Natural Science Foundation of China (82030031, 92149301, 82401082), Chinese Academy of Medical Sciences Research Unit (2019–12M-5-031), Beijing Municipality Government grants (Beijing Laboratory of Oral Health-PXM2021_014226_000041, Beijing Scholar Program-PXM2021_014226_000020), Innovation Research Team Project of Beijing Stomatological Hospital, Capital Medical University (CXTD202201), the State Key Laboratory of Oral Diseases Open Fund (SKLOD2023OF11), Young Scientist Program of Beijing Stomatological Hospital, Capital Medical University (YSP202308). The schemes were created with BioRender.

Data available statement

NA

Author contribution

S.W. guided and revised the manuscript. X.L. and Z.C. wrote the manuscript, M.C. revised the manuscript. The author(s) read and approved the final manuscript.

Ethics approval and consent

NA

Consent for publication

All authors agree to publish.

Conflicts of interest

Author Songlin Wang is the Editor-in-Chief of this journal, but he is not involved in the peer-review or decision of this article.

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