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Review

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The Nrf2 signaling pathway and its molecular regulatory mechanism

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Abstract: Nuclear factor erythroid 2-related factor 2 (Nrf2) is a crucial transcription factor that orchestrates the expression of genes involved in antioxidant defense, detoxification, and the maintenance of cellular homeostasis. This review provides a comprehensive analysis of the dual regulatory role of Nrf2 in both normal physiological and pathological conditions, focusing on the molecular mechanisms by which it modulates mitochondrial function, oxidative stress, inflammation, and autophagy. The review summarizes the current knowledge on the effects of various synthetic and natural compounds, such as flavonoids and resveratrol, on Nrf2 activity. The review also explores the therapeutic potential of Nrf2 in neurodegenerative diseases, cancer, diabetes, and other disorders, laying a foundation for the development of Nrf2-targeted pharmacological interventions.

Key words: Nuclear factor erythroid 2-related factor 2 (Nrf2); Kelch-like ECH-associated protein 1 (Keap1); Oxidative stress; Mitochondrial function; Inflammation; Autophagy

1 Introduction

The maintenance of homeostatic equilibrium is essential for organismal survival, yet exogenous environmental stressors invariably perturb cellular function. Organisms rely on specific regulatory mechanisms to cope with these challenges. Central to this adaptive response is the transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2), which orchestrates cellular protection against oxidative insult. Nrf2 regulates the expression of genes involved in the production of antioxidant enzymes, detoxification processes, and redox homeostasis, thereby helping cells adapt to stress and minimize oxidative damage. In addition to its antioxidative functions, Nrf2 modulates diverse cellular processes including DNA repair mechanisms, autophagic pathways, metabolic regulation, and mitochondrial dynamics (Schmidlin et al., 2021). Aberrant Nrf2 signaling contributes to the pathogenesis of neurodegenerative, cardiovascular, metabolic, inflammatory, oncological, and chronic obstructive pulmonary disorders (COPD). This is because oxidative stress, mitochondrial dysfunction, and inflammation constitute the cardinal pathophysiological mechanisms underlying these disease entities. Elucidating the regulatory mechanisms of Nrf2 activity and its broadening functional repertoire poses significant challenges for targeted therapeutic development while concurrently offering substantial opportunities for treating diverse disease states (Zgorzynska et al., 2021).

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2 Structure of the Nrf2 gene and protein

The human Nrf2 protein is encoded by the NFE2L2 gene, which maps to cytogenetic band 2q31.2 on chromosome 2. According to the NCBI GenBank database, NFE2L2 spans base pairs 177,227,595 to 177,392,697, while more recent data from the AceView database places it on the reverse strand of chromosome 2q31.2, between 178,257,419 and 178,083,605 base pairs, with a total length of 173.81 kb. The NFE2L2 gene comprises 40 distinct introns, encoding 38 mRNA variants, including 31 alternatively spliced forms and seven unspliced transcripts (Ulasov et al., 2022). Further analysis indicates that 22 of these variants are translatable, generating 19 distinct protein isoforms. These isoforms exhibit distinct 5′- and 3′-untranslated region configurations, splice junction architectures, and exon–intron boundary organizations, underpinning the complex transcriptional and post-transcriptional regulation of Nrf2 (Huang et al., 2023).

The Nrf2 protein comprises six highly conserved domains (Neh1–Neh6), each contributing to different aspects of cellular regulation. The Neh1 domain contains a basic leucine zipper (bZIP) structural motif, which is essential for DNA binding and heterodimerization with small Maf (SMAF) proteins. The Neh2 domain harbors two critical motifs (ETGE and DLG) that mediate interaction with Kelch-like ECH-associated protein 1 (Keap1), the principal regulator of Nrf2 degradation under basal conditions. Neh3, Neh4, and Neh5 domains are indispensable for transcriptional activation: Neh3 recruits chromatin-modifying complexes, while Neh4 and Neh5 serve as transactivation domains that assemble transcriptional cofactors. The Neh6 domain contains two degron sequences (DSGIS and DSAPGS) that facilitate Keap1-independent, β-transducin repeat-containing protein (β-TrCP) -mediated ubiquitination and proteasomal degradation, particularly during oxidative stress. Finally, the Neh7 domain negatively modulates Nrf2 activity through retinoic acid receptor α binding, thereby inhibiting the recruitment of transcriptional coactivators (Fig. 1) (He et al., 2020; Zgorzynska, et al., 2021).

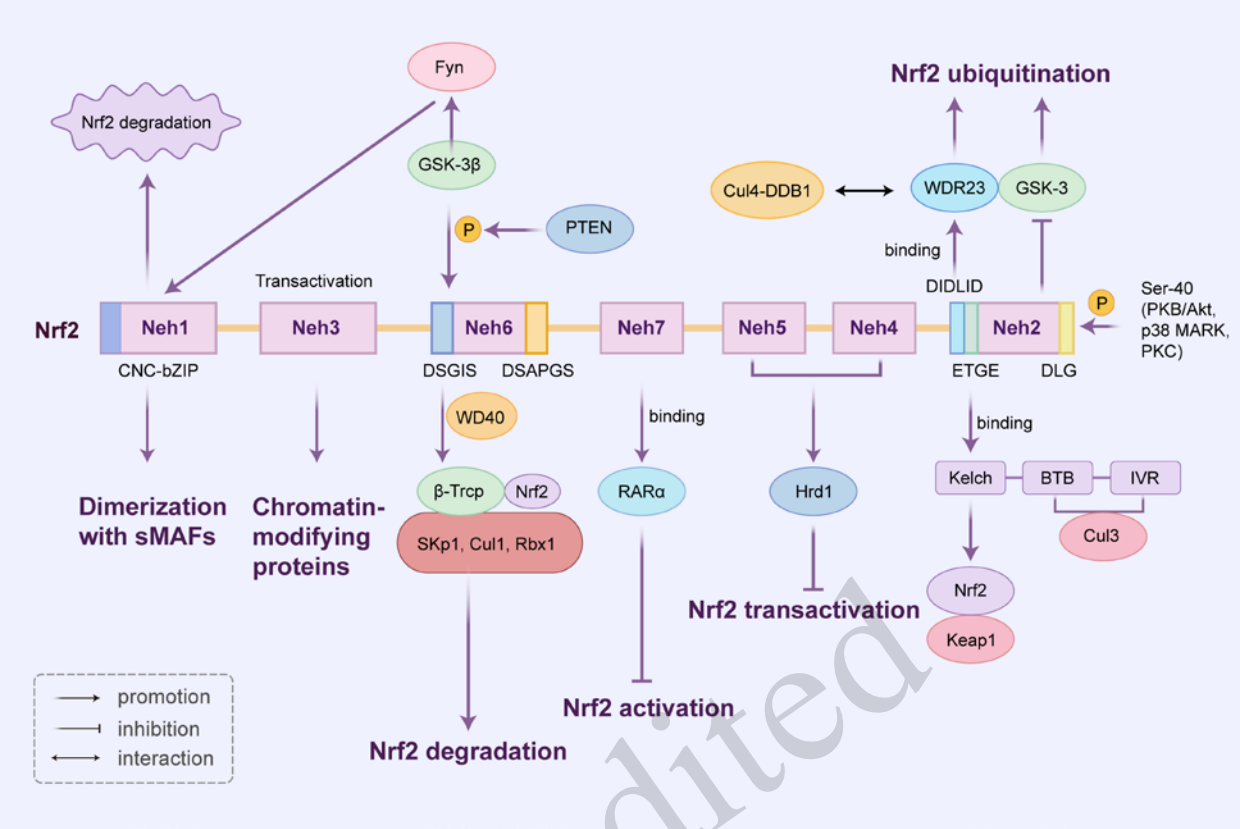

Fig. 1 Six domains of Nrf2 and their functions. Nrf2, nuclear factor erythroid 2-related factor 2; CNC-bZIP, Cap'n'Collar basic leucine zipper; Fyn, tyro-sine-protein kinase Fyn; GSK-3β, glycogen synthase kinase-3β; PTEN, phosphatase and tensin homolog; WD40, WD-repeat protein; β-TrCP, β-transducin repeat-containing protein; Skp1-Cul1-Rbx1, E3 ubiquitin ligase; RARα, retinoic acid receptor α; Hrd1, HMG-CoA reductase degradation 1; Cul4-DDB1, ubiquitin ligase; WDR23, a WD40-repeat protein; BTB, Bric-à-brac, Tramtrack, Broad Complex; IVR, intervening region; Cul3, Cullin 3; Ser-40, Serine 40; PKB, protein kinase B; p38 MARK, p38 mitogen-activated protein kinase; PKC, protein kinase C

3 Nrf2 signaling pathway activation mechanism

The Nrf2 signaling pathway undergoes activation via canonical and non-canonical mechanisms. In the predominant Keap1/Nrf2/antioxidant response element (ARE) regulatory axis, Keap1 functions as a substrate adaptor for the Cullin3-Rbx1 E3 ubiquitin ligase complex, targeting Nrf2 for constitutive ubiquitination and proteasomal degradation under basal conditions. Oxidative stressors or electrophilic compounds induce post-translational modifications of Keap1's cysteine sensor residues, disrupting Keap1–Nrf2 binding. Stabilized Nrf2 subsequently accumulates cytoplasmically and translocates to the nucleus. There, Nrf2 heterodimerizes with small Maf proteins and binds AREs in regulatory regions of target genes, transactivating cytoprotective enzymes essential for antioxidant defense and phase II detoxification. This orchestrated response confers cellular protection against oxidative insult mediated by reactive oxygen species (ROS) and ionizing radiation (Oh and Jun, 2017; Huang, et al., 2023).

The activation of the Keap1/Nrf2/ARE signaling pathway is regulated not only through ubiquitination but also by multi-level mechanisms that control Nrf2 localization, trafficking, and stability. Nrf2's cellular distribution is dynamic, as it can shuttle between the nucleus, cytoplasm, and mitochondrial membrane. This distribution is influenced by processes such as Keap1-mediated degradation and signaling pathways that promote Nrf2's nuclear translocation. This spatial regulation critically depends on key mediators: ubiquitin-conjugating enzyme E2 E3 (UBE2E3) facilitates intracellular trafficking, while importin 11 (IPO11)

governs nuclear translocation efficiency. Collectively, these coordinated mechanisms ensure Nrf2 stabilization and transcriptional competence for optimal oxidative stress responses (Zgorzynska, et al., 2021).

Nrf2 stability is stringently modulated at transcriptional and post-transcriptional levels. Transcriptionally, Nrf2 expression is augmented via an autoregulatory positive feedback loop involving ARE-like sequences (Miao et al., 2005). The NFE2L2 promoter contains CpG-rich islands, wherein hypermethylation suppresses transcriptional activity, thereby reducing Nrf2 abundance (Zgorzynska, et al., 2021). This multifaceted regulatory architecture ensures precise control of Nrf2 signaling, which is essential for maintaining cellular redox equilibrium and orchestrating effective antioxidant responses.

Post-transcriptional regulation of Nrf2 involves pivotal microRNA-mediated mechanisms that target Nrf2 mRNA for degradation (O'brien et al., 2018). Recent investigations with oxygen-glucose deprivation/reperfusion (OGD/R) models demonstrate that miR-380-5p potentiates Nrf2/Keap1 pathway activation by directly repressing Bric-à-brac, Tramtrack, Broad Complex (BTB) and Cap'n'Collar (CNC) homology protein 1 (Bach1) and Bach2, which are transcriptional competitors of Nrf2 for ARE genomic loci (Wang and Xu, 2021). Furthermore, miR-152-3p overexpression enhances Nrf2/ARE signaling by directly inhibiting postsynaptic density protein 93 (PSD-93), a Fyn kinase activator responsible for promoting Nrf2 degradation. This modulation alleviates OGD/R-induced neuronal damage, highlighting the neuroprotective role of miRNA-mediated Nrf2 regulation (Zhang et al., 2019). Post-translational modifications—including phosphorylation, acetylation, and SUMOylation—allosterically modulate the structural and functional interaction between Nrf2 and its principal regulatory partner Keap1 (Huang et al., 2015). These modifications can influence Nrf2 stability by altering its susceptibility to proteasomal degradation, thereby impacting its intracellular levels and availability for executing its protective cellular functions.

Non-canonical activation mechanisms involve additional signaling pathways and specific protein interactions (Huang, et al., 2015). The p62/ Sequestosome 1 (SQSTM1) protein directly interacts with Keap1, disrupting the Keap1–Nrf2 complex and stabilizing Nrf2. This stabilization facilitates the cytosolic accumulation of Nrf2 and its consequent nuclear translocation (Komatsu et al., 2010). The tumor suppressor breast cancer susceptibility 1 (BRCA1) engages Nrf2 via direct protein–protein interaction, shielding it from Keap1-mediated ubiquitin-proteasomal degradation while enhancing its transactivation potential. PALB2 (partner and localizer of BRCA2) amplifies this stabilization by disassembling the Keap1- Cullin 3 (Cul3) E3 ubiquitin ligase complex, thereby potentiating Nrf2 activation (Yi et al., 2021). Pharmacological agents, including sulforaphane, bardoxolone methyl, and curcumin, activate Nrf2 through covalent adduction of reactive cysteine sensor residues within Keap1. This modification disrupts Keap1-mediated Nrf2 ubiquitination, facilitating Nrf2 stabilization (Bahar et al., 2017).

Nrf2 stability and activity are modulated by intersecting signaling cascades. The phosphatidylinositol 3-kinase (PI3K)/AKT pathway phosphorylates and inhibits GSK-3β, attenuating β-TrCP-mediated Nrf2 degradation and oxidative insults. Extracellular signal-regulated kinase (ERK), p38 mitogen-activated protein kinase (p38), and c-Jun N-terminal kinase (JNK) stabilize Nrf2 via site-specific phosphorylation (Joo et al., 2016). Protein kinase C (PKC) phosphorylates Serine 40 (Ser-40) within the Neh2 domain, while casein kinase 2 phosphorylates serine/threonine residues in Neh4 and Neh5 domains. Collectively, they enhance Nrf2 nuclear translocation and transactivation capacity (Bloom and Jaiswal, 2003). Although p38 MAPK phosphorylates Nrf2, its contribution to transcriptional activation remains constrained, indicating indirect regulatory functions (Bloom and Jaiswal, 2003; Best et al., 2018). Additionally, silent mating-type information regulation 2 homolog-1 (SIRT1) enhances Nrf2 stability by reducing its ubiquitination and promoting its nuclear accumulation, further supporting its role in oxidative stress responses (Park et al., 2018). These non-canonical regulatory mechanisms establish a supplementary tier of Nrf2 control, suggesting novel therapeutic targets for pathophysiological conditions associated with oxidative stress and redox dysregulation (Fig. 2).

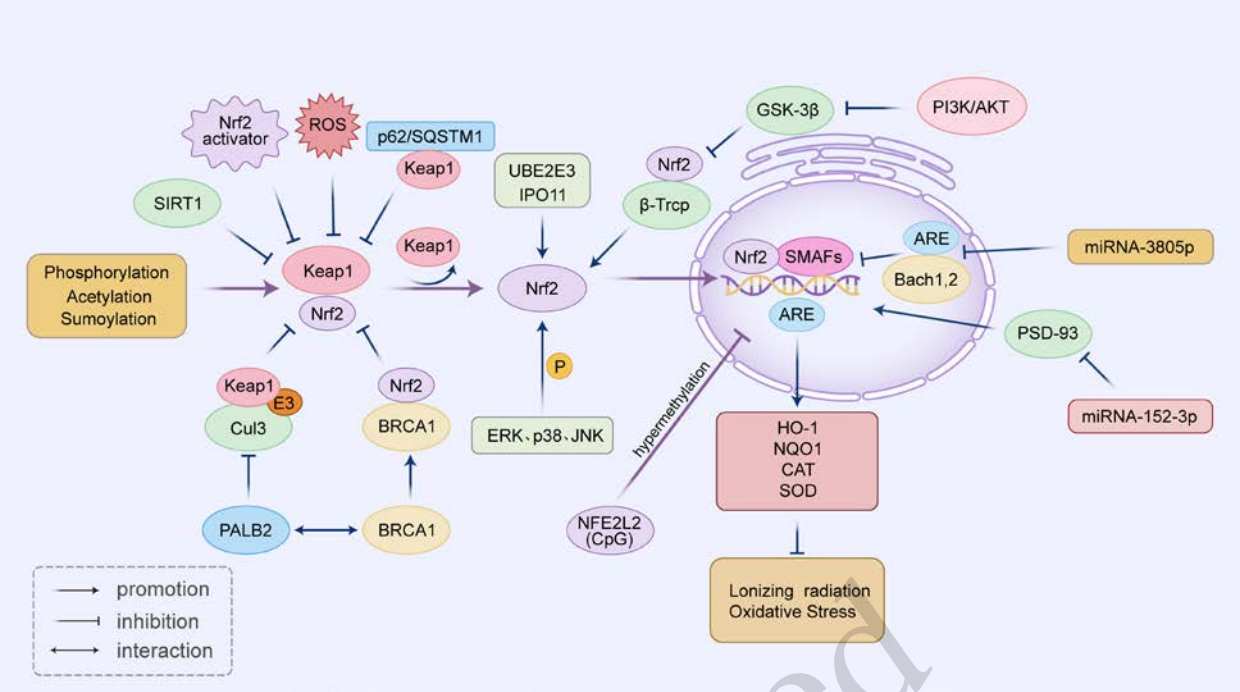

Fig. 2 Activation and stabilization mechanism of Nrf2 signaling pathway. SIRT1, silent mating-type information regulation 2 homolog-1; Nrf2, nuclear factor erythroid 2-related factor 2; ROS, reactive oxygen species; Keap1, Kelch-like ECH-associated protein 1; p62/SQSTM1, sequestosome 1; Cul3, cullin-3; PALB1, partner and localizer of BRCA1; BRCA1, breast cancer susceptibility 1; UBE2E3, ubiquitin-conjugating enzyme E2 E3; IPO11, importin 11; ERK, extracellular signal-regulated kinase; p38, p38 mitogen-activated protein kinase; JNK, c-Jun N-terminal kinase; CpG, cytosine-phosphate-guanine; β-TrCP, β-transducin repeat-containing protein; SMAFs, small musculoaponeurotic fibrosarcoma proteins; ARE, antioxidant response element; HO-1, heme oxygenase-1; NQO1, NAD(P)H quinine oxidoreductase; CAT, catalase; SOD, superoxide dismutase; Bach1/2, two Bric-à-brac, Tramtrack, Broad complex and Cap'n'Collar homology protein1/2; PSD-93, postsynaptic density protein 93.

4 Regulation of Nrf2 by ubiquitin and proteasome degradation

Nrf2 degradation is orchestrated by multiple E3 ubiquitin ligase complexes through both Keap1-dependent and Keap1-independent mechanisms. The Keap1-Cul3-RBX1 complex constitutes the principal E3 ligase governing constitutive Nrf2 turnover under basal conditions. In contrast, Keap1-independent degradation involves other pathways, such as the β-TrCP-SKP1-Cul1-RBX1 complex, Hrd1, and the WDR23-Cul4-damaged DNA binding protein 1 (DDB1) complex. These alternative systems contribute to Nrf2 degradation under specific cellular conditions and environmental stressors (Zhao et al., 2015).

In the canonical Keap1-dependent degradation pathway, Keap1 serves as the primary sensor and regulator of Nrf2 turnover. Keap1 has three functionally critical domains: the BTB domain and the Intervening Region (IVR), which recruit Cul3 to form the Cullin-RING ubiquitin ligase complex, and the Kelch domain, which specifically binds to the Neh2 domain of Nrf2 (Iso et al., 2016; He, et al., 2020). Under basal conditions, Keap1 constitutively facilitates Nrf2 polyubiquitination and proteasomal degradation. During oxidative or electrophilic stress, covalent modifications of specific Keap1 cysteine residues disrupt Nrf2 binding. This enables Nrf2 stabilization, nuclear translocation, dimerization with SMAFs, and subsequent activation of cytoprotective genes via AREs (Kobayashi et al., 2004; Hast et al., 2013; Liu et al., 2018).

The Keap1-independent GSK-3β/β-TrCP axis orchestrates Nrf2 degradation through GSK-3β-mediated phosphorylation of the DSGIS phosphodegron motif. This post-translational modification facilitates β-TrCP

recognition via its WD40 domain and subsequent assembly of the Skp1-Cul1-Rbx1 E3 ubiquitin ligase complex, ultimately targeting Nrf2 for degradation (Rada et al., 2011; Chowdhry et al., 2013). The PTEN may further enhance GSK-3β-mediated phosphorylation of the DSGIS motif in Nrf2, amplifying this degradation pathway (Rojo et al., 2014). Conversely, kinases, including protein kinase B (PKB), p38 MAPK, and PKC, phosphorylate Ser-40 within Nrf2's Neh2 domain and inhibit GSK-3β through N-terminal phosphorylation, enhancing Nrf2 stability and expanding its functional pool (Hayes et al., 2015). Additionally, GSK-3β activation facilitates the nuclear accumulation of Fyn kinase, which phosphorylates Nrf2's Neh1 domain. This promotes the nuclear output of Nrf2, enabling its subsequent ubiquitin-mediated proteasomal degradation (Jain and Jaiswal, 2007). Cell-based ubiquitination assays reveal that Hrd1 attenuates Nrf2 signaling through cytosolic binding to its Neh4 and Neh5 domains, resulting in the suppression of transactivation capacity (Wu et al., 2014). Furthermore, WDR23 mediates the post-translational stabilization of Nrf2 by binding the DIDLID motif within its Neh2 domain and engaging the Cul4-DDB1 ubiquitin ligase complex (Fig. 1).

5 Nrf2 regulates mitochondria, oxidative stress, inflammation, and autophagy to exert protective effects

Nrf2 serves as a central regulator of mitochondrial homeostasis and cytoprotective responses. It orchestrates mitochondrial biogenesis through transcriptional upregulation of mitochondrial transcription factor A (TFAM), which governs mitochondrial DNA replication and transcription (Li et al., 2017a). Nrf2 further promotes ubiquitin-mediated mitophagy through transcriptional induction of PTEN-induced putative kinase 1 (PINK1) and Parkin, enabling selective autophagic clearance of depolarized mitochondria. Concurrently, Nrf2-inducible antioxidant enzymes attenuate mitochondrial ROS generation, thereby preserving membrane potential and oxidative phosphorylation efficiency (Cores et al., 2020). These coordinated mechanisms sustain bioenergetic capacity while preserving mitochondrial structure and function under both homeostatic and pathophysiological conditions.

Nrf2 mediates anti-inflammatory cytoprotection by transcriptionally repressing pro-inflammatory mediators such as interleukin-6 (IL-6) and interleukin-1 beta (IL-1β). In microglia, Nrf2 activation reduces the production of neurotoxic mediators. In Alzheimer's disease (AD), it attenuates amyloid-β genesis by suppressing β-site APP cleaving enzyme 1 (BACE1), thereby reducing amyloid plaque and neurofibrillary tangle formation (Yi et al., 2023). Similarly, in Parkinson's disease (PD), Nrf2 mitigates pathological α-synuclein aggregation and preserves dopaminergic neuron viability (Huang et al., 2020). In amyotrophic lateral sclerosis (ALS), Nrf2 enhances motor neuron viability by reducing proteotoxic stress from misfolded TDP-43/ superoxide dismutase (SOD1) aggregates while augmenting autophagic flux (Soejima-Kusunoki et al., 2022).

Nrf2 orchestrates the transcriptional regulation of autophagy, an essential cellular proteostatic mechanism. It enhances autophagic flux by modulating the expression of core autophagy machinery genes, including ATG family members and p62/SQSTM1, which mediate the clearance of damaged organelles, protein aggregates, and depolarized mitochondria. The p62–Keap1 interaction establishes a critical autoregulatory amplification circuit: p62 sequesters competitive Keap1, liberating and stabilizing Nrf2, while Nrf2 transcriptionally activates p62 expression. This reciprocal regulation amplifies autophagic capacity, enhancing proteostatic competence and cellular stress adaptation (Yi, et al., 2023). Nrf2 also promotes lysosome biogenesis via transcription factor EB (TFEB), accelerating misfolded protein clearance. These coordinated mechanisms reduce oxidative stress, inflammation, protein aggregation, and mitochondrial dysfunction—characteristic pathological features of neurodegenerative disorders. Elucidation of these Nrf2-mediated pathways informs targeted therapeutic development for neurodegenerative pathologies (Yu et al., 2022) (Fig. 3).

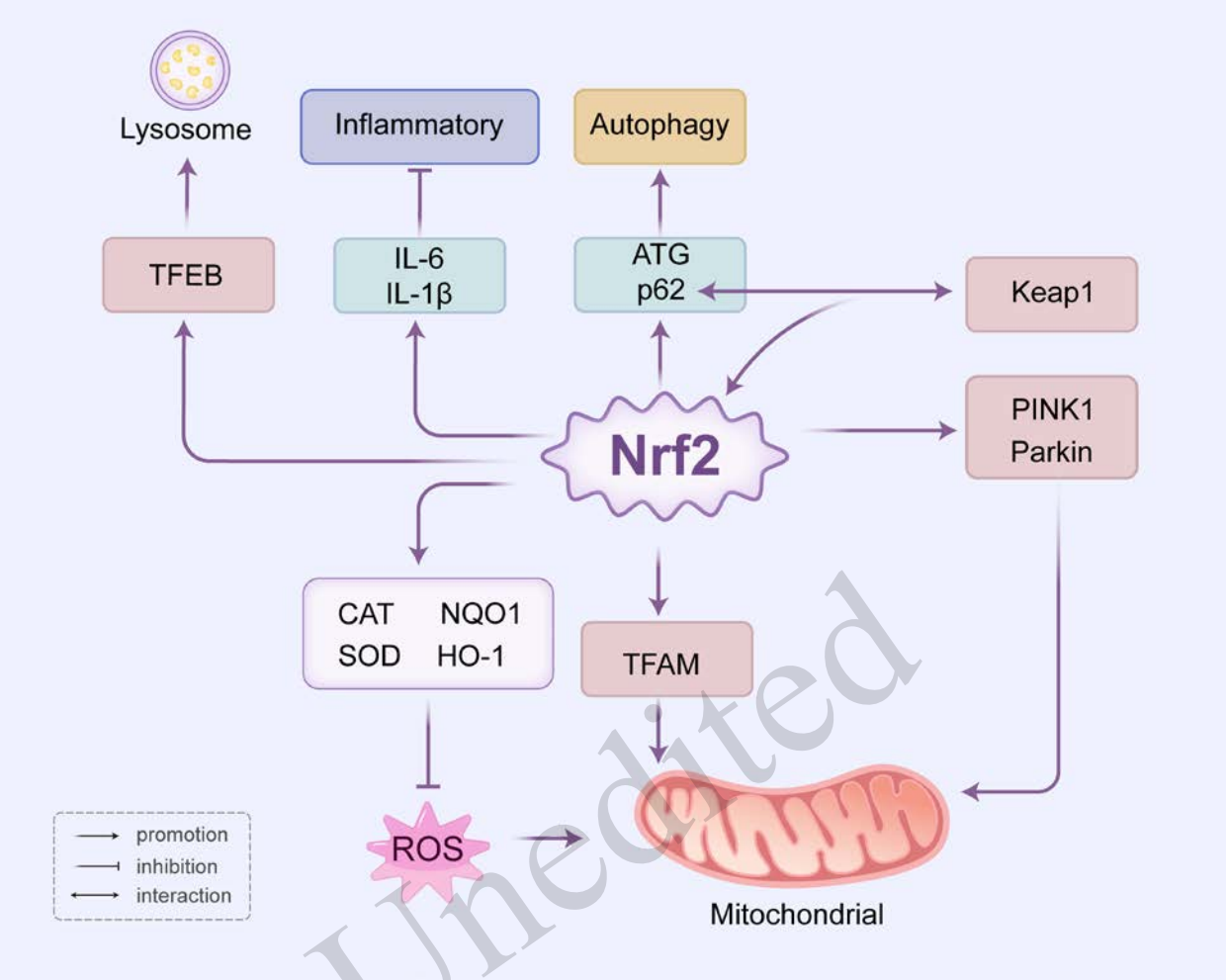

Fig. 3 Regulatory effects of Nrf2 on mitochondrial function, oxidative stress, neuroinflammation, and autophagy. TFEB, transcription factor EB; IL-6, interleukin-6; IL-1β, interleukin-1 beta; CAT, catalase; NQO1, NAD(P)H quinone dehydrogenase 1; SOD, superoxide dismutase; HO-1, heme oxygenase-1; ATG, ATG family, autophagy-related genes; P62, sequestosome 1; Nrf2, nuclear factor erythroid 2-related factor 2; TFAM, mitochondrial transcription factor A; Keap1, Kelch-like ECH-associated protein 1; PINK1, PTEN-induced putative kinase 1; Parkin, Parkin RBR E3 ubiquitin protein ligase.

6 Nrf2 mechanisms and signal regulation by natural and chemically synthesized drugs

Diverse natural and synthetic compounds have been extensively investigated as pharmacological modulators of the Nrf2 signaling axis, which orchestrates pivotal cytoprotective responses. Substances such as sulforaphane, bardoxolone methyl, tert-butylhydroquinone, resveratrol, curcumin, catechins, genistein, diallyl trisulfide, and epigallocatechin gallate have been identified as effective natural activators. Synthetic compounds like oltipraz also stimulate this pathway (Yi, et al., 2021).

Flavonoids represent potent Nrf2 activators, primarily due to their antioxidant and anti-inflammatory pharmacophores. Their bioactive aglycone moieties induce Nrf2 nuclear translocation, demonstrating therapeutic potential in mitigating oxidative stress and inflammation. Genistein, a principal phytoestrogen abundant in legumes, significantly modulates the Nrf2 pathway. Empirical data indicate that genistein enhances both transcription and translation of Nrf2-governed cytoprotective enzymes—notably heme oxygenase-1 (HO-1), cyclooxygenase-2, and inducible nitric oxide synthase—through phosphorylation of the PI3K p85

subunit. This activation of PI3K p85 phosphorylation contributes to mitigating neuronal damage and alleviating β-amyloid peptide-mediated oxidative stress in astrocytes, thereby exerting a protective effect on cells (Guo et al., 2021). Beyond conferring neuroprotection, genistein activates the Nrf2 pathway to mitigate oxidative damage in the cardiovascular system, impeding cardiovascular disease pathogenesis. Under specific conditions, genistein inhibits tyrosine kinase activity, diminishing phospho-Nrf2 nuclear accumulation and attenuating Nrf2/ARE signaling (Liang et al., 2018).

Catechins and their partial derivatives (e.g., resveratrol, oxalic acid) activate the Keap1-Nrf2-ARE pathway by interacting with cysteine residues of Keap1, thereby dissociating the Keap1-Nrf2 complex. This liberation facilitates Nrf2 nuclear translocation and subsequent transcriptional activation of cytoprotective genes encoding antioxidant and detoxification enzymes. Consequently, catechin-mediated Nrf2 signaling elevates the expression and catalytic activity of multiple antioxidative enzymes, establishing a comprehensive intracellular cytoprotective network that effectively counteracts oxidative insults. In lipopolysaccharide-induced PD models, activated Nrf2 restores dopamine and gamma-aminobutyric acid levels while reducing glutamate content. Nrf2 activation antagonizes nuclear factor kappa-B (NF-κB) signaling, suppressing the synthesis and secretion of pro-inflammatory cytokines including tumor necrosis factor α (TNF-α), IL-1β, and IL-6 (Zhang et al., 2022). In addition, catechins modulate apoptotic pathways via Nrf2 activation, elevating anti-apoptotic protein expression while suppressing pro-apoptotic protein activity, reducing the rate of cell apoptosis (Shen et al., 2024). This mechanism of action helps to protect cells from apoptotic death induced by harmful external stimuli such as oxidative stress, inflammatory reactions, etc., as well as to maintain tissue stability and function.

Luteolin, a flavonoid ubiquitous in plant-derived foods, exhibits potent anti-inflammatory, antioxidant, and antitumorigenic properties (Zhu et al., 2024). Luteolin activates Nrf2 signaling, elevating antioxidant enzyme expression, including HO-1, thereby attenuating pathological progression in blue light-induced retinal degeneration and hyperuricemic nephropathy (Yu et al., 2024; Hayakawa et al., 2025). However, when acting as an inhibitor, luteolin suppresses Nrf2 activation by upregulating p47phox and p22phox expression, inducing aberrant ROS accumulation and apoptosis in HT29 colon carcinoma cells (Yang et al., 2020). At physiological concentrations, it potentiates the chemosensitivity of A549 lung adenocarcinoma cells to oxaliplatin, bleomycin, and doxorubicin. siRNA-mediated Nrf2 knockdown abrogates luteolin-induced chemosensitization, indicating that pharmacological Nrf2 inhibition may potentiate therapeutic responsiveness to chemotherapeutic agents (Tang et al., 2011).

Resveratrol (RSV), a non-flavonoid polyphenolic compound, represents a naturally occurring phytoalexin biosynthesized by plants upon exposure to environmental stressors. It stabilizes the Nrf2 protein by inhibiting its ubiquitin-mediated degradation and facilitating its nuclear translocation, enabling Nrf2 to function as a transcription factor. RSV administration in an AD murine model exerts neuroprotective effects and enhances survival, which is attributed to the attenuation of amyloid-β accumulation and the suppression of tau protein hyperphosphorylation (Porquet et al., 2013). RSV further activates the PI3K/Akt signaling cascade, inducing serine phosphorylation of Nrf2. This post-translational modification disrupts the Nrf2-Keap1 complex, facilitating Nrf2 nuclear translocation and the subsequent transactivation of ARE-regulated genes (Hui et al., 2018). Nrf2 upregulates the expression of phase II detoxifying enzymes and antioxidants, including glutathione peroxidase (GSH-Px) and SOD, significantly augmenting cellular antioxidant defense systems and mitigating oxidative stress-induced damage. This regulatory pathway is integral to cell survival, proliferation, and metabolic homeostasis. RSV extends its protective effects beyond antioxidative activity by exerting significant anti-inflammatory properties. This action is mediated through Nrf2-dependent pathways, resulting in the inhibition of key inflammation mediators such as nuclear factor kappa B (NF-κB). Consequently, RSV attenuates the synthesis and secretion of pro-inflammatory cytokines and mediators, thereby facilitating the resolution of inflammatory cascades (Xia et al., 2024).

Sulforaphane (SFN), an isothiocyanate derived from cruciferous vegetable glucosinolates, functions as an electrophilic compound that covalently modifies key cysteine residues within Keap1. This modification disrupts

the Keap1-Nrf2 protein–protein interaction, enabling Nrf2 to evade Keap1-mediated ubiquitination and proteasomal degradation, facilitating its nuclear accumulation. Following nuclear translocation, Nrf2 dimerizes with small Maf proteins and binds to ARE, transactivating the expression of phase II detoxifying enzymes such as GST, uridine diphosphate glucuronosyltransferase, and NAD(P)H Quinone Dehydrogenase 1 (NQO1). Concurrently, SFN indirectly inhibits the activity of phase I enzymes by modulating the Nrf2 pathway, thereby reducing the metabolic conversion of pro-carcinogens into carcinogens. SFN also enhances cellular antioxidant capacity by promoting the synthesis of antioxidants such as glutathione (GSH), further strengthening the cell's defense against oxidative stress (Chen et al., 2024a). Beyond its chemopreventive properties, SFN facilitates the detoxification of harmful substances, including pesticide residues and heavy metals, by activating Nrf2-regulated detoxification enzymes. These enzymes convert toxic compounds into water-soluble, less toxic metabolites, which are subsequently excreted via the liver or kidneys. SFN suppresses inflammatory pathways, including the NF-κB signaling axis, through activation of the Nrf2 cascade, resulting in the attenuation of pro-inflammatory cytokine production (Ma et al., 2023).

Tert-butylhydroquinone (TBHQ), a synthetic electrophilic compound, is a well-characterized activator of the Nrf2 signaling pathway that has been extensively investigated for its capacity to ameliorate oxidative stress and associated cellular damage (Ujah et al., 2021). TBHQ mediates its effects through the electrophile-mediated covalent modification of specific cysteine residues within Keap1, thereby disrupting Keap1-mediated repression of Nrf2 and facilitating Nrf2 nuclear translocation. Within the nucleus, Nrf2 heterodimerizes with small Maf proteins, binds to ARE, and activates the transcription of cytoprotective enzymes and antioxidants (Baxter et al., 2021). TBHQ demonstrates significant cardioprotective efficacy, particularly against doxorubicin-induced pathophysiological alterations, via Nrf2-dependent attenuation of oxidative damage. The compound further ameliorates ROS generation, exhibiting broad cytoprotection across diverse cellular systems. In H9C2 cardiomyocyte models, TBHQ mitigates oxidative stress, apoptosis, and cellular injury elicited by deleterious agents, including ethanol and xenobiotics (Deng et al., 2021).

Metformin, a low-cost first-line biguanide antidiabetic agent with a favorable safety profile, manifests pleiotropic therapeutic efficacy extending beyond glycemic control to encompass pulmonary fibrosis, oncological conditions, obesity, and hepatopathies (Lv and Guo, 2020). In hyperglycemic models, metformin ameliorates renal inflammatory injury in diabetic murine models through Keap1/Nrf2 pathway modulation and enhanced mitophagy in renal tubular epithelial cell senescence (Sun et al., 2024a). Within oncology, metformin significantly potentiates cisplatin chemosensitivity in gastric carcinoma via Nrf2 suppression, metabolic reprogramming, and concomitant activation of oxidative stress, p53 tumor suppression, and adenosine monophosphate-activated protein kinase (AMPK) signaling cascades (Duan et al., 2025). Clinically, the combination of sorafenib and metformin for the treatment of hepatocellular carcinoma suppresses cancer cell proliferation by inducing ferroptosis through modulation of the p62-Keap1-Nrf2/HO-1 pathway (Tang et al., 2022).

Table 1 Mechanisms of Nrf2 regulation by various drugs

Drug	Mechanism
Genistein	Increasing the phosphorylation of PI3K p85 synergistically enhances the expression of HO-1 at mRNA and protein levels (Huang, et al., 2023)
Catechins	Acting on the Nrf2 pathway, reducing ROS levels, inducing ARE-mediated expression of antioxidant genes, including phase II detoxifying enzymes (Yang et al., 2022)

Luteolin	Keap1/Nrf2/HO-1 signaling pathway; suppressing Nrf2 activation by modulating $p47^{phox}$ and $p22^{phox}$ expression; inducing a decrease in Nrf2 expression, resulting in reduced binding of Nrf2 to ARE; and depletion of reduced glutathione (Tang, et al., 2011; Yang, et al., 2020; Hayakawa, et al., 2025)
Resveratrol	Increasing Nrf2 gene expression; upregulating downstream antioxidant enzymes such as SOD, GPX, and CAT (Majhi et al., 2023)
Sulforaphane	Keap1/Nrf2 pathway, promoting its nuclear translocation; inducing Nrf2/ARE/PRDX6 activity; inducing antioxidant enzyme expression; increasing mitochondrial biogenesis; and preventing dopaminergic neuronal loss (Shore et al., 2024)
Tert-Butylhydroquinone	Keap1/Nrf2 /ARE signal pathway; stimulates transcription of phase 2 genes (Satoh et al., 2009)
Metformin	Keap1/Nrf2 pathway and enhancing mitophagy; suppressing Nrf2 expression and activating p53 and AMPK pathways; Keap1/Nrf2/HO-1 signal pathway (Tang, et al., 2022; Sun, et al., 2024a; Duan, et al., 2025)

PI3K, phosphatidylinositol 3-kinase; HO-1, heme oxygenase-1; ROS, reactive oxygen species; ARE, antioxidant response element; Nrf2, nuclear factor erythroid 2-related factor 2; Keap1, Kelch-like ECH-associated protein 1; SOD, superoxide dismutase; GPX, glutathione peroxidase; CAT, catalase; PRDX6, peroxiredoxin 6; AMPK, adenosine monophosphate-activated protein kinase

7 The regulatory role of Nrf2 in several diseases

Nrf2 is a critical transcription factor that regulates cellular homeostasis by controlling the expression of protective genes involved in antioxidant defense, detoxification, and redox balance. Due to its central role in mitigating oxidative stress and inflammation, the Nrf2 pathway influences the progression of numerous diseases, making it a promising target for therapeutic intervention.

7.1 Neurodegenerative Diseases

Oxidative stress and neuroinflammation are pathophysiological hallmarks of neurodegenerative disorders. In AD models, Nrf2 nuclear translocation within substantia nigra dopaminergic neurons mediates homeostatic regulation of intracellular ROS balance and confers cytoprotection to this vulnerable neuronal population. Decreased nuclear Nrf2 expression is documented in AD, with a recent meta-analysis of microarray datasets identifying 31 downregulated ARE-driven genes in AD patients (Wang et al., 2017). Correspondingly, transgenic AD mouse models demonstrate that enhanced Nrf2 expression and downstream antioxidant enzymes (e.g., HO-1) ameliorate spatial learning deficits and cognitive impairment. These findings underscore Nrf2's potential to mitigate early AD pathological processes, including neuroprotection mediated by the regulation of amyloid-β peptide and phosphorylated tau protein (Yang et al., 2025).

PD manifests as the progressive degeneration of substantia nigra dopaminergic neurons and the accumulation of neuronal inclusion bodies (Lewy bodies) containing ubiquitinated α-synuclein aggregates (Funayama et al., 2023). Proximity proteomics analyses demonstrate that ZNF746 (Paris), a PD-associated zinc finger transcription repressor, significantly downregulates endogenous NQO1 expression. This repression induces oxidative stress and apoptotic cascades, driving dopaminergic neurodegeneration in PD models. Mechanistically, ZNF746 interacts with Nrf2-MAFG heterodimers, repressing ARE-driven cytoprotective gene expression. Pharmacological Nrf2 activation counteracts these pathological processes by attenuating ROS production, inhibiting apoptotic pathways, reducing α-synuclein aggregation, and ultimately conferring neuroprotection (Lapak et al., 2023).

Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder characterized by progressive neuronal loss and the accumulation of mutant huntingtin protein aggregates. An analysis of HD brain tissue revealed elevated oxidative stress markers, mitochondrial dysfunction, and sustained neuroinflammation (Valadão et al., 2020). Nrf2-deficient mice are more susceptible to the effects of mitochondrial complex II inhibitors 3-nitropropionic acid (3-NP), while Nrf2 overexpression confers striatal neuroprotection against 3-NP and malonate toxicity (Shih et al., 2005; Hamouda et al., 2024). Pharmacological activation of the Nrf2/ARE pathway by synthetic triterpenoids upregulates endogenous antioxidant defenses, including cerebral HO-1 expression; reduces lipid peroxidation biomarkers such as MDA; ameliorates motor deficits; and extends survival in transgenic HD murine models (Stack et al., 2010).

ALS is a rapidly progressive and invariably fatal neurodegenerative disorder characterized by the selective degeneration of cortical and spinal motor neurons. Oxidative damage, neuroinflammation, and mitochondrial dysfunction constitute key pathogenic contributors. In $hSOD1^{G93A}$ transgenic murine models, mutant SOD1 expression induces profound oxidative stress that suppresses total Nrf2 expression and impedes its nuclear translocation. This impairment downregulates the glutamate-cystine antiporter SLC7A11 and glutathione peroxidase 4 (GPX4), thereby potentiating ferroptosis in motor neurons. Pharmacological activation of Nrf2 abrogates ferroptosis and confers neuroprotection in both in vitro and in vivo ALS models (Yang et al., 2023). Complementary investigations demonstrate that in the $hSOD1^{G93A}$ mouse model, desloratadine administration exerts multifaceted protective effects through the 5HTR2A/cAMP/AMPK signaling axis by promoting autophagy to reduce mutant hSOD1 levels, suppressing oxidative stress via the downstream Nrf2-HO-1/NQO-1 pathway, and inhibiting astrocyte-mediated neuroinflammation through the NF-κB/NOD-like receptor family pyrin domain containing (NLRP3) cascade in the spinal cord (Lu et al., 2024).

7.2 Cancer

In breast cancer murine models, Nrf2 activity is principally orchestrated by its epigenetic regulator zinc finger MYND-type containing 8 (ZMYND8). ZMYND8 enhances Nrf2 stability by mitigating Keap1-mediated ubiquitination, impeding Nrf2 proteasomal degradation. It recruits Nrf2 to the promoters of antioxidant genes, leading to their increased expression, reduced iron levels within breast cancer stem cells (BCSCs), and the protection of BCSCs from oxidative stress and ferroptosis. The critical interaction between the PBP domain of ZMYND8 and the Neh1 domain of Nrf2 facilitates direct binding and mutual regulation. Furthermore, Nrf2 can enhance ZMYND8 transcription by binding to the ARE located on the ZMYND8 promoter, establishing a positive feedback loop. This regulatory mechanism underscores Nrf2's dual role in promoting antioxidant defense and maintaining BCSC survival. Therefore, a critical investigation is warranted to examine whether ZMYND8-mediated Nrf2 activation within BCSCs promotes therapeutic resistance in breast cancer (Luo et al., 2024a).

In prostate cancer (PCa) cellular models, Nrf2 regulation is principally mediated through the SPOP (speckle-type POZ protein)–p62 interaction axis. SPOP functions as a substrate recognition component of the Cullin 3-RING E3 ubiquitin ligase complex, with frequent mutations observed in prostate carcinogenesis. Conversely, p62—a multifunctional scaffolding protein integral to selective autophagy and stress response pathways—exhibits pathological elevation in diverse disease states and modulates Nrf2 activation through competitive Keap1 sequestration. Structural analyses establish that SPOP's MATH domain directly engages the SBC motif of p62. Under normal physiological conditions, SPOP facilitates the non-degradable ubiquitination of p62, thereby negatively regulating p62-mediated sequestration of Keap1 and suppressing Nrf2-mediated stress responses. However, recurrent SPOP mutations abrogate this regulatory function. This molecular dysfunction promotes the pathological accumulation of p62, enhances autophagic flux, and sustains aberrant Nrf2 pathway activation (Shi et al., 2022).

Nrf2 demonstrates a biphasic regulatory function in pulmonary carcinogenesis, exhibiting tumor-suppressive or oncogenic activity modulated by disease progression stage. During initial tumorigenesis in pulmonary neoplasia murine models, Nrf2 exerts cytoprotective effects by sustaining cellular redox homeostasis, regulating phase II detoxification enzyme expression, preventing genomic instability, mediating cell cycle control, and inhibiting pro-inflammatory cascades. Nrf2 facilitates the progression of established tumors, whether the activation mechanism is pharmacological or genetic (Kalpana Deepa Priya et al., 2011; Tao et al.,

2018). Non-small cell lung carcinoma (NSCLC) exhibits frequent Nrf2/Keap1 pathway mutations resulting in aberrant activation. This sustained Nrf2 upregulation confers cytoprotective advantages to malignant cells, consequently underpinning the development of chemoresistance in NSCLC (Chen et al., 2014).

7.3 Diabetes

Gestational diabetes mellitus (GDM) is a pregnancy-specific metabolic disorder characterized by insulin resistance, the unmanaged progression of which has profound adverse repercussions for both maternal health and fetal-neonatal outcomes across perinatal and lifelong timescales. Hyperglycemic conditions downregulate Nrf2 expression while significantly upregulating miR-142-5p in human trophoblastic BeWo cells. Notably, there is a strong inverse correlation between miR-142-5p levels and Nrf2 expression in GDM patients. This dysregulation leads to a marked decrease in the expression of Nrf2-regulated antioxidant genes, including NQO1, SOD, and catalase (CAT), as well as decreased angiogenic markers such as HIF-1α and SDF. The suppression of miR-142-5p may restore Nrf2 activity, thereby promoting placental angiogenesis in GDM (Milan et al., 2024). N-acetyl-L-cysteine-mediated activation of the Nrf2/HO-1 signaling axis in GDM murine liver tissue ameliorates oxidative stress, inflammatory responses, and hyperlipidemia, thereby attenuating gestational complications and improving reproductive outcomes (Wang et al., 2023).

Type 1 diabetes mellitus (T1DM) is a chronic autoimmune disorder characterized by the immune-mediated destruction of pancreatic β-cells, which results in absolute insulin deficiency and persistent hyperglycemia (Li et al., 2017b). In alloxan-damaged MIN6 β-cells, formononetin competitively binds Keap1 to activate the cytoprotective Nrf2 pathway, suggesting that it may have therapeutic potential for mitigating oxidative stress in T1DM pathogenesis (Chen et al., 2024b). Urolithin C administration in non-obese diabetic (NOD) mice significantly suppresses Keap1 expression and activates the Nrf2 antioxidant pathway, upregulating NQO1 and HO-1. This intervention improves β-cell functional integrity and preserves normoglycemia and insulin homeostasis, thereby attenuating T1DM pathogenesis (Luo et al., 2023).

Type 2 diabetes mellitus (T2DM) is a multifactorial, chronic, and complex metabolic disorder influenced by genetic predisposition, family history, age, lifestyle, and dietary habits (Ortiz-Martínez et al., 2022). Under high glucose and high fat conditions, poliumoside treatment of bone mesenchymal stem cells has been shown to enhance Nrf2 nuclear translocation. This activation consequently induces the transcriptional upregulation of the cytoprotective enzymes HO-1 and GPX4, thereby attenuating ferroptosis and promoting the biosynthesis of osteogenic regulatory proteins (Xu et al., 2024). In streptozotocin-induced T2DM mouse models, treatment with gentisic acid significantly increases p21 gene expression while reducing the binding of Keap1 to Nrf2. This interference decreases Nrf2 ubiquitination and subsequent degradation, thereby enhancing the activation of the antioxidant redox signaling pathway (Razliqi et al., 2023).

7.4 Cardiovascular Diseases

Atherosclerosis (AS) features lipid deposition in the arterial intima, forming uneven plaques. These induce lumen narrowing, impaired compliance, and fibrotic vessel walls. Using micheliolide (MCL) pretreatment in both ox-LDL combined macrophages and $ApoE^{-/-}$ mice, the results demonstrated that MCL increased the transcriptional activity of GPX4 and xap5 circadian timekeeper (xCT) by activating the Nrf2 pathway, thereby inhibiting macrophage ferroptosis. Simultaneously, MCL competitively inhibits Keap1 at Arg483, inducing dissociation of the Keap1/Nrf2 complex. This facilitates Nrf2 nuclear translocation and attenuates AS (Luo et al., 2024b). In AS mouse models, itaconate exerts anti-atherosclerotic effects in vivo by inducing Nrf2 activation, which results in the downregulation of proinflammatory cytokine and chemokine expression and secretion, the inhibition of macrophage infiltration, and the suppression of inflammatory polarization (Song et al., 2023b).

Hypertension is a prevalent cardiovascular disease that imposes significant global health burdens. Chronic microinjection of 5-Aminoimidazole-4-carboxamide ribonucleotide into the rat hypothalamic paraventricular nucleus activates the AMPK/Nrf2 axis, downregulating NADPH oxidase 2 (NOX2) /NOX4 expression, reducing ROS production, and upregulating SOD1 expression. This activation also reduces TNF-α expression while increasing IL-10 levels, ultimately lowering plasma norepinephrine levels. These combined effects reduce systolic blood pressure and ameliorate hypertension (Fu et al., 2024). In $Nrf2^{+/+}$ mice, the

co-administration of angiotensin II (to induce oxidative stress) and TBHQ for 12–14 days activates Nrf2, upregulating dimethylarginine dimethylaminohydrolase (DDAH)-1 and DDAH-2 gene expression. This reduces ROS levels, promotes nitric oxide (NO) production, and metabolizes asymmetric dimethylarginine, thereby inhibiting NO synthase (NOS). The inhibition of NOS reduces the production of endothelial-derived contraction factors, mitigating microvascular hyperreactivity to thromboxane A2 and endothelin-1. In $Nrf2^{-/-}$ mice, these protective effects are abolished, demonstrating that Nrf2 mediates protection against microvascular endothelial dysfunction and pathological hypertension induced by angiotensin II (Wang et al., 2018).

7.5 Respiratory Diseases

In acute lung injury (ALI), inflammatory cascades and oxidative stress mediate accumulating intracellular iron ions and lipid peroxidation, triggering ferroptosis and pulmonary tissue damage. In mouse models of intestinal ischemia-reperfusion (IIR)-induced acute lung injury, characteristic features of ferroptosis are observed, including decreased GSH and GPX4 levels, increased MDA expression, and Nrf2 activation. Nrf2 knockdown accelerates ferroptosis, suppresses the expression of TERT and SLC7A11, and exacerbates lung tissue damage. These findings suggest that Nrf2 may mitigate ferroptosis in IIR ALI by regulating TERT and SLC7A11 expression levels (Dong et al., 2021). In murine models of sepsis-induced acute lung injury, supplementation with 4-octyl itaconate (4-OI) rescues attenuated Nrf2/HO-1 signaling, elevates GPX4 expression, suppresses PTGS2, and reduces MDA and intracellular iron levels, protecting against pulmonary injury (He et al., 2022).

Chronic cigarette smoke exposure in COPD induces pulmonary iron deposition, oxidative stress, and inflammation, culminating in lung tissue damage. Nrf2 counteracts this progression by suppressing ferroptosis through ROS scavenging and GSH biosynthesis to maintain redox homeostasis. Murine studies demonstrate that smoke-exposed lungs exhibit increased Fe^{3+} deposition, diminished Nrf2 and GPX4 expression, alveolar space enlargement, and airflow limitation. Nrf2 induction upregulates GPX4 and SOD expression, reduces ROS accumulation, and inhibits pro-inflammatory cytokine (e.g., IL-1β, IL-8) release. These findings establish that Nrf2/GPX4 axis activation mitigates ferroptosis and inflammatory cascades, thereby attenuating COPD-associated pulmonary parenchymal damage (Zhang et al., 2021).

7.6 Inflammatory Diseases

Rheumatoid arthritis (RA) is a chronic autoimmune disorder characterized by synovial hyperplasia, pannus formation, and progressive bone/cartilage destruction, ultimately causing functional disability and joint deformity (Smolen et al., 2016). Genetic ablation of the Nrf2 transcriptional repressor Keap1 activates the Nrf2 pathway, suppressing pro-inflammatory cytokines (IL-6, IL-1β, TNF-α, CCL2) and upregulating antioxidant enzymes in SKG murine joint tissues, thereby attenuating arthritis progression. The synthetic triterpenoid CDDO-Im, administered orally, elicits both prophylactic and therapeutic effects in SKG mice through Nrf2-dependent mechanisms (Zhang et al., 2023a). In synovial tissues of RA, lysine acetyltransferase 2A (KAT2A)-mediated histone H3 lysine 9 acetylation constrains Nrf2 activation, driving unchecked pro-inflammatory cytokine IL-1β production and promoting inflammatory pathogenesis. Consequently, pharmacological inhibition of KAT2A represents a promising therapeutic strategy for RA management (Zhang et al., 2023b).

Inflammatory bowel disease (IBD) is a chronic relapsing-remitting gastrointestinal disorder characterized by intestinal inflammation with multifactorial etiology involving mucosal immunity, environmental triggers, and host genetics (Sahoo et al., 2023). In DSS-induced murine colitis models, Ginkgo biloba-derived nanoparticles significantly induce p62 upregulation. p62 sequesters Keap1, liberating Nrf2 from cytoplasmic retention. Subsequent Nrf2 nuclear translocation transactivates cytoprotective genes, including HO-1 and GCLM, attenuating oxidative damage, enhancing cytoprotection, and modulating mucosal immunity to promote epithelial restitution (Yang et al., 2024).

7.7 Chronic Kidney Disease

Chronic kidney disease refers to a group of kidney disorders caused by primary kidney diseases, various secondary kidney diseases, and congenital and hereditary kidney conditions. In erastin-treated HK2 cells, vi-

texin competitively inhibits Keap1, preventing Nrf2 ubiquitination and proteasomal degradation, activating the Nrf2/HO-1 signaling pathway. This transcriptional activation upregulates GPX4 expression, subsequently inhibiting lipid peroxidation and ferroptosis (Song et al., 2023a). Diabetic nephropathy is one of the most significant complications of diabetes. In Nrf2 knockout mice with diabetic kidney disease (DKD), the downregulation of GSH synthesis and transferases, along with the increase of 8-OHdG (a marker of oxidative stress), exacerbates renal oxidative stress. This results in mesangial expansion, glomerular capillary enlargement, and heightened inflammation characterized by the overexpression of CCL2, IL-6, and MCP-1, leading to macrophage infiltration and further cytokine release. These changes aggravate DKD progression, causing renal cortical thinning and fibrosis. Nrf2 dysfunction exacerbates DKD pathogenesis, whereas pharmacological restoration of Nrf2 activity confers renoprotection by attenuating disease progression (Liu et al., 2022). In DKD murine models, mitoQ administration upregulates Nrf2 expression/activity, induces PINK1 transcription, attenuates oxidative cytotoxicity, and restores mitochondrial homeostasis (Xiao et al., 2017).

7.8 Liver Diseases

Non-alcoholic fatty liver disease (NAFLD) is a clinicopathological entity characterized by excessive hepatocellular lipid deposition in the absence of significant alcohol intake or other defined hepatic insults. Danshen Zexie decoction ameliorates high-fat-diet-induced murine NAFLD via Nrf2 activation, suppressing reactive oxygen species generation, reducing NLRP3 inflammasome assembly, and inhibiting pro-caspase-1 autocleavage into active caspase-1 (Biao et al., 2022). In vitro free fatty acid-induced NAFLD models demonstrate that garcinia cambogia activates the Nrf2/ARE pathway, reduces oxidative stress, suppresses lipogenic transcription factors C/EBPα and PPARγ, and decreases lipid accumulation and apoptosis (Han et al., 2021).

Viral hepatitis is an infectious inflammatory liver disease caused by hepatotropic viruses that potentially progresses to acute/chronic hepatic dysfunction with severe sequelae, including cirrhosis and hepatocellular carcinoma. The hepatitis B virus (HBV) X protein competitively disrupts Keap1-Nrf2 binding, while Nrf2 overexpression enhances its occupancy at the HBV core promoter region, significantly attenuating promoter activity and viral replication (Ariffianto et al., 2023). A study of liver biopsy specimens from 24 patients with chronic hepatitis C revealed that TGF-β1 enhances GSK-3β activity, which subsequently modulates Nrf2 as its homologous substrate. This regulation promotes Nrf2 nuclear translocation and degradation, impairing antioxidant responses and exacerbating hepatic injury. Consequently, GSK-3β-targeted therapy may exert hepatoprotective effects in hepatitis by enhancing Nrf2-mediated antioxidant responses (Jiang et al., 2015).

Cirrhosis represents a major global health burden with diverse etiological factors including obesity, NAFLD, chronic excessive alcohol consumption, hepatitis B and C infections, autoimmune disorders, cholestatic diseases, and pathological iron or copper accumulation. In carbon tetrachloride-induced hamster models, curcumin administration activates the Nrf2 signaling axis, suppressing NF-κB expression and inflammatory cytokine production while conferring hepatoprotection (Macías-Pérez et al., 2019). In bile duct ligation-induced cirrhotic murine models, Nrf2 protein expression is significantly downregulated. Naltrexone treatment substantially increases Nrf2 levels, enhancing its mediated antioxidant responses and attenuating hepatic fibrogenesis (Hosseini-Fard et al., 2022).

7.9 Aging

Aging is intricately associated with cumulative oxidative damage and cellular dysfunction. The Nrf2 pathway—a principal regulator of cytoprotective responses—experiences progressive age-related decline, with diminishing cellular capacity to maintain redox homeostasis and repair oxidized macromolecules, including proteins, nucleic acids, and lipids. The enhancement of Nrf2 signaling has been proposed as a promising strategy for mitigating aging-related processes, improving mitochondrial function, reducing inflammation, and potentially preventing the onset of age-related degenerative diseases (Sun et al., 2020). An aging model was established using D-galactose to induce senescence in both mice and HT22 cells. Vitamin D administration activates the Nrf2/HO-1 axis via vitamin D receptor signaling, attenuating NLRP1 inflammasome activation. This mechanism mitigates ferroptosis-mediated hippocampal neurodegeneration and cognitive decline in aging murine models (Guo et al., 2022). In vitro UVB-irradiated human dermal fibroblasts and subsequent in vivo validation demonstrate that salvianolic acid B activates PI3K signaling while suppressing IL-17/MAPK pathways. This dual action promotes Nrf2 nuclear translocation and the transcriptional activation of antioxidant genes, enhancing ROS clearance in photoaging models (Sun et al., 2024b).

8 Conclusion

Nrf2 functions as a master transcriptional regulator that orchestrates cellular homeostasis by modulating antioxidant defense mechanisms, metabolic pathways, inflammatory responses, autophagic flux, and mitochondrial biogenesis. Its activity is dynamically regulated by multiple determinants such as activating signals, cell type-specific factors, protein interactions, and crosstalk with other transcriptional networks. Under physiological conditions, Nrf2 activation typically mediates cytoprotective effects. However, in cancer biology, this protective mechanism can be co-opted to support tumor survival and progression. This pathway also exhibits a dual role during viral infection, potentially leading to either host-protective or pathogen-advantageous outcomes. Future research should focus on clarifying the mechanisms by which the Nrf2-dependent signaling pathway transitions from providing physiological benefits to promoting pathological conditions. Elucidating this mechanistic shift may provide critical insights into the pathogenesis of diverse disease pathologies.

Data availability statement

It is not applicable to this article as no new data were created or analyzed in this study.

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Author contributions

Handong Fan and Rong Chen contributed to the conception and design of the review. Yunfei PAN and Xiaodong Zhang wrote the first draft of the manuscript and created all the figures. Yimin Lu and Hao Qin critically revised the manuscript. All authors have read and approved the final manuscript.

Compliance with ethics guidelines

Handong Fan, Rong Chen, Yunfei PAN, Xiaodong Zhang, Yimin Lu and Hao Qin declare that they have no conflict of interest.

This article does not contain any studies with human or animal subjects performed by any of the authors.

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