

Overview of regulatory mechanisms of NRF2 signal pathways in ferroptosis and tumor progression

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Abstract

Oxidative stress, characterized by an imbalance between the production of reactive oxygen species (ROS) and cellular antioxidant defenses, is a critical driver of various pathological states. The transcription factor nuclear factor erythroid 2-related factor 2 (NRF2) serves as the master regulator of redox homeostasis, counteracting oxidative stress by orchestrating the expression of genes involved in glutathione biosynthesis, iron metabolism, and lipid peroxidation detoxification. Recently, the specific induction of lipid peroxidation has been identified as the hallmark of ferroptosis, a form of regulated cell death that represents a promising vulnerability for cancer therapy. However, cancer cells frequently hijack the NRF2 pathway to suppress ferroptosis, thereby promoting tumor survival, metastasis, and therapy resistance. Here, we comprehensively summarize the multi-layered regulatory mechanisms of NRF2, spanning transcriptional, post-transcriptional, and post-translational modifications, within the specific context of the ferroptosis-cancer axis. We further discuss how aberrant NRF2 signaling confers ferroptosis resistance in malignancy and highlight emerging therapeutic strategies that target the NRF2 pathway to reignite ferroptotic cell death in tumors. A deeper understanding of these regulatory networks is essential for the development of precision ferroptosis-based cancer therapies.

Keywords: NRF2, ferroptosis, transcription, co-factors, epigenetics, post-translational modifications, histone modifications, tumor progression, and cancer therapy

1. Introduction

Reactive oxygen species (ROS) are chemically reactive molecules that are essential for the survival of living organisms^[1]. Owing to the distinct regulatory mechanisms and metabolism rewiring, cancer cells exhibit increased endogenous ROS levels, rendering them more vulnerable to ROS-mediated stress compared to normal cells^[2,3]. Consequently, manipulating ROS levels represents a potential therapeutic strategy to induce tumor cell death while sparing normal tissues^[4]. However, redox imbalance in cancer cells is highly complicated because of the various regulators that are involved in. In response to oxidative stress, cells adapt by modulating the activity and expression of multiple transcription factors. These factors constitute an antioxidant barrier that mitigates potential damage caused by ROS overload. A key player in this process is nuclear factor erythroid 2-related factor 2 (NRF2; encoded by *NFE2L2*), the master transcriptional regulator of the antioxidant response, as the majority of its downstream targets are dedicated to maintaining redox homeostasis.

The most critical signaling protein within the NRF2-regulated pathway is Kelch-like ECH-associated protein 1 (KEAP1), which functions as a repressor and degrader of NRF2. KEAP1 contains multiple cysteine residues that act as sensors for oxidative or electrophilic stress, inducing conformational changes that lead to NRF2 escape from ubiquitin-proteasome degradation^[5,6]. Under physiological conditions, this mechanism maintains cellular homeostasis. However, in the context of malignancy, the system is frequently hijacked. Notably, advanced-stage cancer cells frequently harbor gain-of-function mutations in *NFE2L2* or loss-of-function



mutations in *KEAP1*, leading to the constitutive activation of NRF2. These mutations are prevalent across various cancer types, particularly in non-small cell lung cancer (NSCLC)^[7]. The inactivation of *KEAP1* or the expression of mutant NRF2 results in the nuclear accumulation of NRF2 and the subsequent upregulation of its target genes. While this reduces intracellular ROS levels and enhances ROS-scavenging capacity to promote cell survival, the implications of constitutive NRF2 activation extend far beyond oxidative stress management. This phenomenon, often described as the “dark side” of NRF2, fosters a permissive environment for tumorigenesis through several distinct mechanisms, with a particular emphasis on the evasion of ferroptotic cell death^[8].

Iron-dependent ROS accumulation promotes ferroptosis, a novel form of regulated cell death triggered by an overload of lipid peroxides. Notably, many proteins and enzymes involved in preventing lipid peroxidation, and thus inhibiting the initiation of ferroptosis, are encoded by NRF2 target genes. Consequently, NRF2 plays an indispensable role in regulating lipid peroxidation and ferroptosis^[9]. Although ferroptosis was initially identified through high-throughput screening of anti-tumor agents, mounting evidence indicates that it represents a targetable vulnerability in cancer^[10–13]. Given that NRF2 activity is directly linked to ferroptosis sensitivity, NRF2 itself, its regulators, and its downstream targets offer promising avenues for ferroptosis-based cancer therapies. The following sections review the direct non-genomic regulatory mechanisms of NRF2 activation. Furthermore, we highlight the potential roles of NRF2 regulators in oxidative stress and ferroptosis, discussing their impact on tumorigenesis and implications for cancer therapy.

2. KEAP1-NRF2 Signaling Pathway

NRF2 activity is strictly controlled by internal and external stimuli associated with oxidative stress. Under basal conditions, *KEAP1* acts as an adaptor linking NRF2 to the Cullin-3 (CUL3)-based E3 ligase complex, mediating NRF2 degradation via the ubiquitin-proteasome pathway in the cytoplasm^[5]. In response to oxidative and electrophilic stress, specific sensor cysteine residues on *KEAP1* (Cysteine 151, Cysteine 273, Cysteine 288) undergo modification. This induces a conformational change in *KEAP1*, preventing degradation of NRF2 and facilitating the translocation of NRF2 from the cytoplasm to the nucleus to drive antioxidant gene expression^[6,14,15]. Thus, *KEAP1* functions as a negative regulator of the NRF2 oxidative stress response pathway.

Nuclear NRF2 forms heterodimers with small musculoaponeurotic fibrosarcoma (sMAF) proteins (MAFF, MAFK, and MAFG) and binds to antioxidant response elements (AREs), specifically the core sequence 5'-TGACNNGC-3', to activate the expression of a broad spectrum of cytoprotective genes^[16–19]. These target genes are involved in diverse cellular processes, including the antioxidant response, detoxification, cellular metabolism, survival, proliferation, autophagy, DNA repair, and mitochondrial physiology^[20–22]. Although significant scientific progress has been made, challenges remain in effectively targeting NRF2, its regulators, or its downstream effectors.

3. Genomic Dysregulation of the KEAP1-NRF2 Pathway

The *KEAP1*-NRF2 signaling pathway is frequently co-opted by cancer cells, where constitutive NRF2 activation confers advantages in tumor growth, metastasis, and chemoresistance^[23,24]. Although *NFE2L2* or *KEAP1* mutations occur less frequently than common drivers like *KRAS* or *TP53*, genetic alterations in this pathway are found in approximately 20% of lung adenocarcinoma (LUAD) and 20–30% of lung squamous cell carcinoma (LUSC) cases, representing one of the largest definable subsets of LUSC^[25,26]. Most *NFE2L2* alterations observed in LUSC are gain-of-function mutations. These are generally mutually exclusive with *KEAP1* mutations and typically localize to the high-affinity binding DLG and ETGE motifs. Meanwhile, an increased *NFE2L2* gene copy number has also been described in LUSC^[27]. Conversely, *KEAP1* mutations are distributed throughout the gene but often affect functional domains, consistent with its role as a tumor suppressor. Loss-of-function mutations in *KEAP1* were first identified in NSCLC but have since been reported in hepatocellular, colorectal, breast, prostate, ovarian, and gallbladder carcinomas. These mutants result in constitutive NRF2 activation, increased nuclear target gene expression, and altered redox homeostasis. The prevalence of these mutations underscores the critical role of oxidative stress in tumorigenesis.

4. The Role of NRF2-Regulated Ferroptosis in Cancer Progression

Ferroptosis, first identified by Dixon *et al.* in 2012, is a form of regulated cell death characterized by excessive lipid peroxidation of cellular membranes, resulting from a disrupted antioxidant defense system and/or imbalanced cellular metabolism. To date, several ferroptosis defense mechanisms have been discovered, with the cyst(e)ine/glutathione (GSH)/glutathione peroxidase 4 (GPX4) axis serving as the core system. GPX4 protects cells from ferroptosis by reducing lipid hydroperoxides to lipid alcohols, utilizing GSH as a cofactor^[28]. Ferroptosis induced by GPX4 inhibition depends on the activity of acyl-CoA synthetase long-chain family member 4 (ACSL4), which acylates free fatty acids, such as polyunsaturated fatty acids (PUFAs). Subsequently, lysophosphatidylcholine acyltransferase 3 (LPCAT3) incorporates these acylated fatty acids into phospholipids^[29,30].

NRF2 acts as a master regulator coordinating multiple aspects of ferroptosis, including iron metabolism, GSH synthesis, and ROS detoxification, through the transcriptional upregulation of numerous genes^[9,31] (Figure 1). Extensive studies have demonstrated that most direct target genes of NRF2 function as ferroptosis suppressors to promote cancer progression.

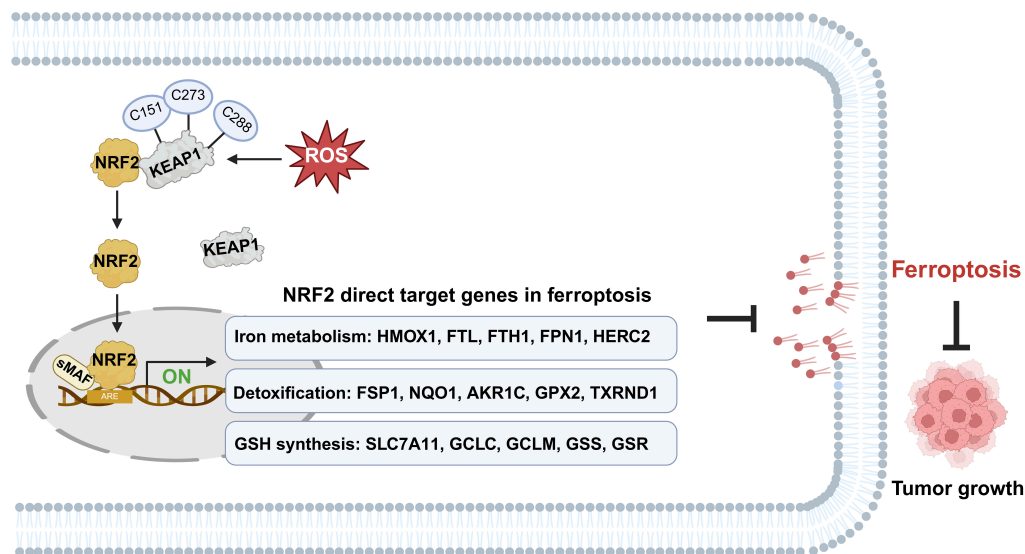


Figure 1. The crucial role of NRF2 in ferroptosis defense. Upon exposure to ROS-induced oxidative stress, NRF2 protein is stabilized in KEAP1-dependent manner and translocates from the cytoplasm to the nucleus. Nuclear NRF2 heterodimerizes with sMAF proteins and binds to AREs within the promoter regions of target genes. This transcriptional program orchestrates a multi-layered defense against ferroptosis by upregulating genes governing iron metabolism, detoxification, and GSH synthesis. Created in [BioRender.com](https://www.biorender.com). ROS: reactive oxygen species; NRF2: nuclear factor erythroid 2-related factor 2; sMAF: small musculoaponeurotic fibrosarcoma; AREs: antioxidant response elements; GSH: glutathione; KEAP1: Kelch-like ECH-associated protein 1.

4.1 Iron metabolism

Heme oxygenase 1 (HO-1; encoded by *HMOX1*) plays a dual role in ferroptosis, contingent upon its level of activation. Excessive HO-1 activation catalyzes heme degradation, producing large amounts of free iron. This iron overload induces lipid peroxidation and accelerates ferroptosis via the Fenton reaction, as observed in hepatocellular carcinoma (HCC) cells^[32,33]. Conversely, HO-1 can also exert antioxidant effects that inhibit ferroptosis, contributing to radioresistance in glioblastoma (GBM), through the production of heme metabolic byproducts, including biliverdin and carbon monoxide^[34,35]. Thus, the activation of HO-1 may play distinct, context-dependent roles in cancer progression.

4.2 Detoxification

GPX4 is a critical molecule preventing lipid peroxidation and the occurrence of ferroptosis. It is established that the ferroptotic response induced by GPX4 inhibitors is ACSL4-dependent^[29]. Interestingly, deficiency of tumor ACSL4 accelerates tumor progression by impairing spontaneous anti-tumor immunity, suggesting that a natural ferroptosis-inducing mechanism functions during tumor development^[36]. It is worth noting that while GPX4 is commonly considered an NRF2 target gene, NRF2 chromatin immunoprecipitation sequencing (ChIP-seq) (ENCODE portal: ENCFF390TMR) and Cleavage Under Targets and Release Using Nuclease (CUT & RUN) data indicate that NRF2 is not significantly enriched at the *GPX4* genomic region^[37,38]. Furthermore, NRF2 knockdown has been shown to upregulate GPX4 expression in lung tumor spheroid cells^[39]. Therefore, *GPX4* may not be a direct transcriptional target of NRF2.

It is well-established that NRF2-null mice show a significantly reduced ability to detoxify aldehydes, leading to an accumulation of toxic metabolites. NRF2 induces the expression of NAD(P)H:quinone oxidoreductase 1 (NQO1), which prevents radical generation and ferroptosis^[40]. In addition, aldo-keto reductases (AKRs, such as AKR1A1-3, AKR1B10, *et al.*) are a superfamily of enzymes that serve as critical downstream targets in the NRF2-mediated detoxification pathway^[41,42]. Due to their broad substrate specificity, AKRs not only neutralize lipid peroxidation products like 4-Hydroxynonenal (4-HNE) and methylglyoxal, but also degrade xenobiotic and chemotherapeutic agents, thereby contributing to chemoresistance in cancer cells^[43].

4.3 GSH synthesis

GSH, the primary cofactor for GPX4, mitigates lipid peroxidation and ferroptosis. The synthesis process begins with the cystine/glutamate antiporter System xc (comprising SLC7A11 and SLC3A2), which imports cystine that is subsequently reduced to cysteine. Next, glutamate and cysteine are ligated by glutamate-cysteine ligase (GCLC/GCLM) to produce the dipeptide γ -glutamyl-cysteine. Under conditions of cystine starvation, GCLC can also exhibit non-canonical activity, utilizing glutamate to produce γ -glutamyl-cysteine to protect against ferroptosis^[44]. Finally, glycine is added to γ -glutamyl-cysteine by glutathione synthase (GSS) to generate the tripeptide GSH. All enzymes in the GSH synthesis pathway (SLC7A11, GCLC/GCLM, GSS) are under NRF2 control.

The essential role of SLC7A11 in providing intracellular cysteine, influencing kynurenine metabolism, and maintaining lysosomal pH homeostasis is critical for preventing ferroptosis and tumor progression^[45-47]. However, ferroptosis sensitivity induced by SLC7A11 expression is context-dependent^[48]. While *Slc7a11* knockout mice are phenotypically normal, embryonic fibroblasts derived from these animals fail to survive in culture without β -mercaptoethanol supplementation, which facilitates cellular cysteine uptake^[49]. Moreover, prolonged treatment with SLC7A11 inhibitors induces ferroptosis resistance in ovarian cancer cells via activation of the transsulfuration pathway, catalyzed by cystathionine β -synthase (CBS) (another direct NRF2 target)^[50]. Since intracellular cysteine can be synthesized via compensatory pathways (such as from methionine via the transsulfuration pathway) in addition to SLC7A11-mediated import^[51], the clinical utility of SLC7A11 inhibitors requires careful consideration.

Given the high frequency of *NFE2L2/KEAP1* mutations leading to constitutive NRF2 activation in cancer, the protective effect of NRF2 overexpression against ferroptosis implies its potential as a biomarker. The involvement of NRF2 activation in regulating ferroptosis was first elucidated in hepatocellular carcinoma cells in 2016^[52]. Treatment with SLC7A11 inhibitors (e.g., erastin) enhances the suppression of NRF2-mediated ferroptosis defense. Over the past decade, research has revealed crucial NRF2-regulated mechanisms in ferroptosis and established its key role in cancer progression. While lipid peroxidation products, including 4-HNE and malondialdehyde (MDA), and expression levels of signature genes, including prostaglandin-endoperoxide synthase 2 (*PTGS2*), ChaC glutathione-specific gamma-glutamylcyclotransferase 1 (*CHAC1*), transferrin receptor 1 (*TFR1*)^[53], and peroxiredoxin 3 (*PRDX3*)^[54] are currently regarded as detection markers for ferroptosis, these markers are context-dependent and subject to other regulatory influences. Notably, there remains a lack of specific biomarkers for definitively detecting ferroptosis *in vivo*, hindering the monitoring of dynamic changes in ferroptosis during cancer progression.

5. Upstream Regulators of NRF2 Activation

Changes in *NFE2L2* mRNA expression and stability contribute to NRF2 overexpression and the induction of its downstream targets. Cellular NRF2 transcript levels are tightly regulated by transcription factors and non-coding RNA (ncRNA) events through transcriptional, epigenetic, post-transcriptional, or post-translational modification pathways.

5.1 Transcriptional and post-transcriptional regulation

Genomic variations can constitutively elevate NRF2 activity in cancer by augmenting *NFE2L2* mRNA levels (Figure 2A). Additionally, activation of endogenous oncogenes, such as myelocytomatosis oncogene (*MYC*)^{ERT2}, b-Raf proto-oncogene, serine/threonine kinase (*BRAF*)^{V619E}, and Kirsten rat sarcoma viral oncogene homolog (*KRAS*)^{G12D}, directly increases the transcription and activity of NRF2 during tumorigenesis^[55]. *MYC* can directly bind to the *NFE2L2* promoter and activate NRF2 transcription to counteract oxidative stress and drive tumor progression of head and neck squamous cell carcinoma (HNSCC)^[56]. Of note, inhibition of SLC7A11, a critical NRF2 target involved in cystine import and GSH synthesis, resulted in tumor suppression and improved overall survival in a *Kras*^{G12D} mutant LUAD mouse model. This model drives the rewiring of GSH metabolism by upregulating NRF2 expression^[57]. Therefore, targeting NRF2-mediated ferroptosis resistance provides a vital avenue for cancer therapy.

Activating transcription factor 4 (ATF4) directly upregulates NRF2 expression in response to the integrated stress response (ISR), which plays a central role in cancer plasticity^[58]. Moreover, activating transcription factor 2 (ATF2) has been found to suppress the anti-tumor effects of bromodomain and extraterminal domain (BET) inhibitors by significantly upregulating NRF2 levels, thereby attenuating ferroptosis^[59]. Yes-associated protein (YAP), a major transcriptional coactivator in the Hippo pathway, also increases NRF2 transcription to bolster tumor cell defense against ferroptosis^[60]. Additionally, deacetylated Y-box protein 1 (YB-1), an RNA-binding protein, exhibits reduced binding to *NFE2L2* mRNA, thereby repressing NRF2 translation to modulate oxidative stress and pro-metastatic activity^[61]. Conversely, SRY (sex determining region Y)-box 17 (SOX17) is a novel upstream transcriptional suppressor of NRF2 to sensitize esophageal squamous cell carcinoma (ESCC) cells to ferroptosis and radiation treatment^[62]. These mechanisms underlying the direct activation of NRF2 in response to diverse stresses offer potential drug combination strategies for treating human cancer (Figure 2B).

5.2 Epigenetic regulation

Oxidative stress response can also be influenced by epigenetic events, which modulate chromatin structure or RNA stability to regulate gene transcription^[63,64] (Figure 2B). Cytosine-phosphodiester bond-guanine (CpG) methylation in *NFE2L2* promoter region is involved in programming NRF2 expression. A recent pilot study indicated that CpG methylation of the *NFE2L2* promoter could serve as a risk factor for age-related lung cancer^[65].

Histone methylation and demethylation at the *NFE2L2* promoter region regulate its transcriptional activity, thereby modulating ROS generation to contribute to drug resistance or carcinogenesis^[66-69] (Figure 2B). A recently reported study demonstrated that Enhancer of Zeste Homolog 2 (EZH2), a transcriptional repressor that catalyzes histone H3K27 trimethylation, maintains H3K27ac marks and recruits transcription factor occupancy at *NFE2L2* promoters to stimulate *NFE2L2* transcription and maintain malignancy^[70]. Inactivation of the facilitates chromatin transcription (FACT) complex, a histone chaperone that facilitates rapid nucleosome disassembly, reduces the transcription elongation of *NFE2L2* and its downstream antioxidant genes, thereby increasing

chemosensitivity^[74]. Furthermore, N6-methyladenosine (m⁶A) methylation is a reversible epigenetic mark that modulates mRNA stability and translation. m⁶A readers can directly bind and stabilize *NFE2L2* mRNA in an m⁶A-dependent manner to promote ferroptosis resistance and tumor suppression^[72-75].

5.3 Non-coding RNA

Given the diversity of physiological processes controlled by NRF2, findings indicate that NRF2 regulation is also guided by ncRNAs, including microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), during cancer progression. Although ncRNAs can function as both downstream targets and upstream regulators of NRF2, we focus here on upstream regulators (Figure 2C,D).

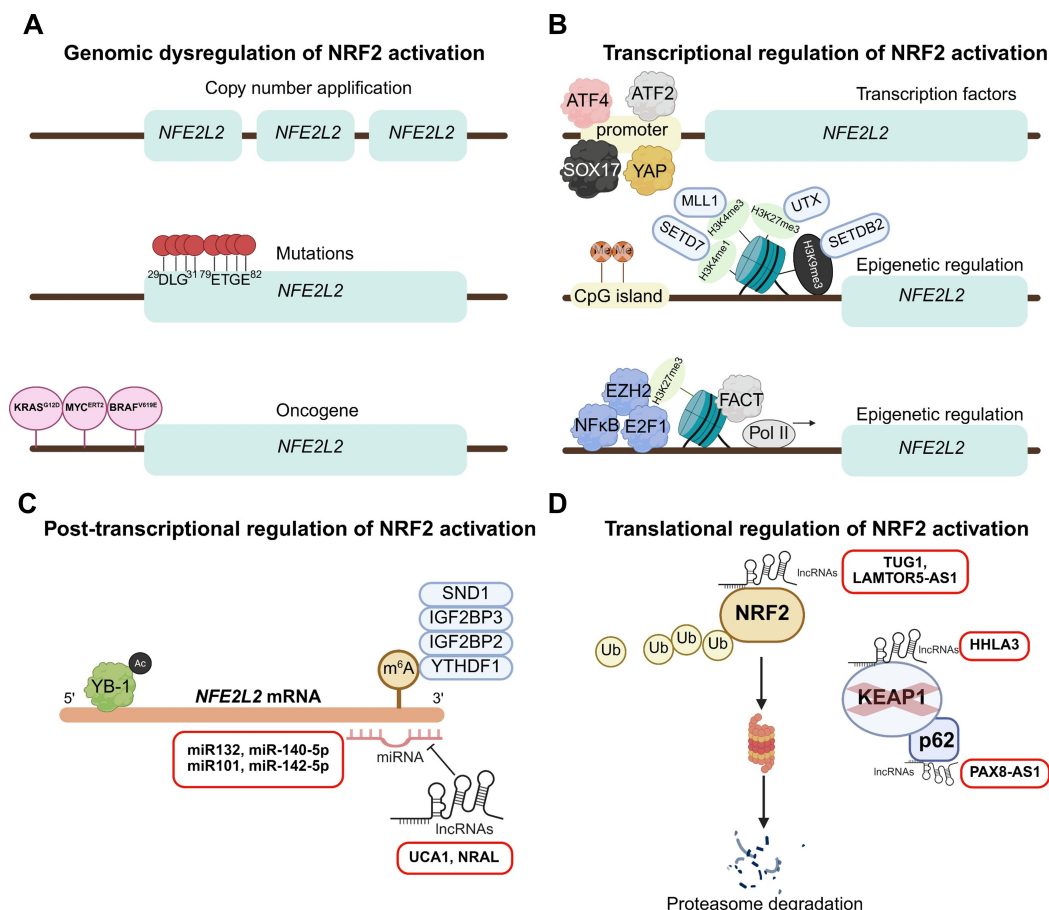


Figure 2. Upstream regulators of NRF2 activation. (A) Genomic alterations driving *NFE2L2* mRNA upregulation. Mechanisms include *NFE2L2* copy number amplification, gain-of-function mutations (predominantly within the DLG and ETGE motifs), and oncogene-induced NRF2 activation; (B) Transcriptional and epigenetic regulation of *NFE2L2*. Transcription factors such as ATF4, ATF2, YAP, and SOX17 modulate NRF2 activation. Epigenetic mechanisms, including CpG island demethylation, histone modifications at the promoter region, and enhanced transcriptional elongation, promote *NFE2L2* mRNA expression; (C) Post-transcriptional regulation of *NFE2L2* mRNA. This includes suppression by microRNAs (miR-132, miR-140-5p, miR-101, and miR-142-5p), modulation by long non-coding RNAs (lncRNAs UCA1 and NRAL), m⁶A RNA methylation readers (SND1, IGF2BP2, IGF2BP3, and YTHDF1), and stabilization by the RNA-binding protein YB-1; (D) Post-translational regulation of NRF2 protein. LncRNAs such as TUG1, LAMTOR5-AS1, HHLA3, and PAX8-AS1 disrupt the NRF2-KEAP1 complex, thereby preventing NRF2 degradation. Created in BioRender.com. NRF2: nuclear factor erythroid 2-related factor 2; ATF4: activating transcription factor 4; ATF2: activating transcription factor 2; YAP: Yes-associated protein; YB-1: deacetylated Y-box protein 1; SOX17: SRY (sex determining region Y)-box 17; CpG: cytosine-phosphodiester bond-guanine; UCA1: Urothelial cancer associated 1; NRAL: NRF2 regulation-associated lncRNA; SND1: staphylococcal nuclease and tudor domain containing 1; IGF2BP2: insulin-like growth factor-2 mRNA-binding protein 2; IGF2BP3: insulin-like growth factor-2 mRNA-binding protein 3; YTHDF1: YTH N6-methyladenosine RNA binding protein 1; LAMTOR5-AS1: late endosomal/lysosomal adaptor, MAPK and MTOR activator 5-antisense RNA 1; TUG1: taurine upregulated gene 1 (TUG1); HHLA3: HERV-H LTR-associating 3; PAX8-AS1: paired box 8-antisense RNA 1.

miRNAs are single-stranded ncRNAs of approximately 22 nucleotides that typically modulate the translation or stability of *NFE2L2* mRNA by binding to specific sequences via complementary base pairing. In the following section, we summarize direct miRNA mediators of NRF2 that contribute to carcinogenesis in response to ROS-induced stress. miR-132, miR-140-5p, miR-101, and miR-142-5p act as oncogenic negative regulators of NRF2 by targeting the 3'UTR of *NFE2L2*, reducing NRF2 expression and thereby regulating tumor metastasis and chemoresistance^[76-79]. Thus, dysregulation of the miRNA-NRF2 machinery significantly influences oxidative stress and tumorigenesis.

lncRNAs (> 200 nucleotides) regulate NRF2 expression through varied mechanisms, including acting as competitive endogenous RNAs (ceRNAs) for proteins or as miRNA sponges, recruiting chromatin modifiers and transcription factors, or mediating translational repression/degradation. Several lncRNAs act as regulators of the NRF2-oxidative stress system. Urothelial cancer associated 1 (UCA1) upregulates NRF2 expression by sponging miR-495, contributing to chemoresistance in NSCLC^[80]. Nrf2 regulation-associated lncRNA (NRAL) acts as a ceRNA for NRF2, binding miR340-5p to activate NRF2, leading to drug resistance in HCC^[81]. Moreover, late endosomal/lysosomal adaptor, MAPK and MTOR activator 5-antisense RNA 1 (LAMTOR5-AS1) or taurine upregulated gene 1 (TUG1) directly binds and stabilizes NRF2 protein, associating with chemoresistance^[82,83]. Meanwhile, KEAP1-mediated degradation of NRF2 is indirectly attenuated by HERV-H LTR-associating 3 (HHLA3) or paired box 8-antisense RNA 1 (PAX8-AS1) to promote cancer progression^[84,85]. Collectively, lncRNA-NRF2 regulation is characterized by tissue specificity, which is relevant to the development of targeted therapies for specific cancer subtypes.

6. Co-Factors of NRF2 Transcriptional Activity

Although NRF2 serves as the master transcription factor directly regulating a series of genes in response to antioxidant stress, studies report that several proteins, including epigenetic regulators and chromatin remodeling complexes, act as co-factors for NRF2. These co-factors modulate specific subsets of target genes without altering the mRNA or protein levels of NRF2.

NRF2 contains seven highly conserved domains known as NRF2-ECH homology (Neh) domains. Among these, the Neh4, Neh5, and Neh3 regions are critical for NRF2 transcriptional activity through binding components of the transcriptional apparatus^[86], such as CBP/p300^[87,88] and CHD6^[89]. Recently, many unexpected co-factors of NRF2 have been identified (Figure 3). These factors cooperate with NRF2 to protect cells from ferroptosis and maintain cell survival.

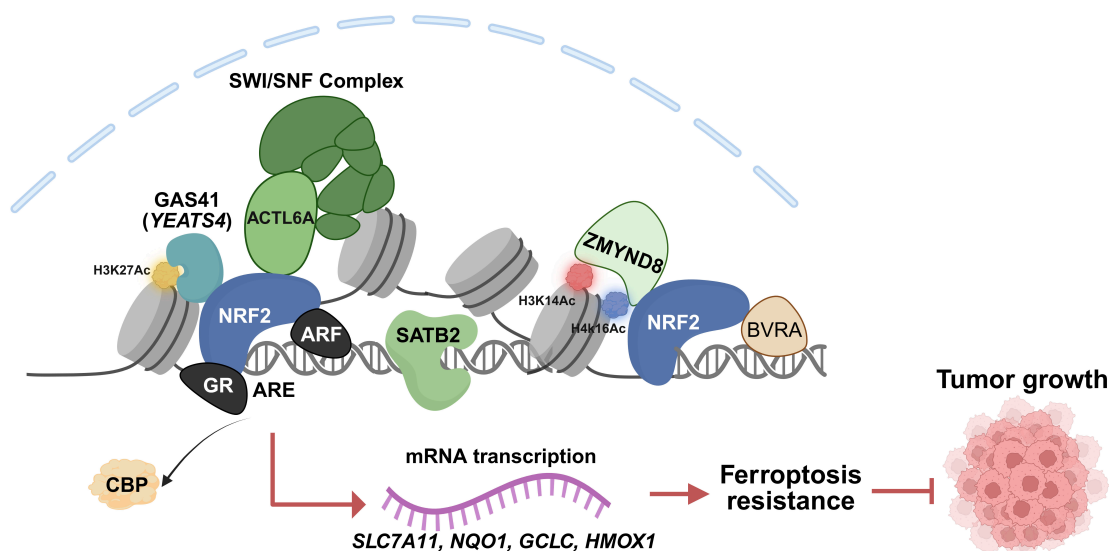


Figure 3. Co-factors modulating NRF2 transcriptional activity. Illustration of the diverse chromatin-associated proteins that interact with NRF2 to fine-tune its transcriptional output. These include transcriptional activators (GAS41, ACTL6A, and ZMYND8), chromatin loop organizers (SATB2), biosynthetic enzyme (BVRA and TIGAR) and transcriptional suppressors (ARF and GR), which enhance or inhibit NRF2 transactivation potential. Created in [BioRender.com](https://www.biorender.com). NRF2: nuclear factor erythroid 2-related factor 2; GAS41: Glioma Amplified Sequence 41; ACTL6A: actin-like protein 6A; ZMYND8: Zinc finger MYND-type containing 8; SATB2: special AT-rich binding protein-2; BVRA: Biliverdin reductase A; TIGAR: TP53 induced glycolysis and apoptosis regulator; ARF: alternative reading frame; GR: glucocorticoid receptor.

We identified Glioma Amplified Sequence 41 (GAS41, encoded by *YEATS4*) as a transcriptional regulator that anchors NRF2 on chromatin. GAS41 enhances the DNA-binding activity of NRF2, regulated by histone markers (H3K27Ac), to promote ferroptosis resistance and tumor progression in NSCLC^[37]. Similarly, actin-like protein 6A (ACTL6A), encoding a SWI/SNF subunit, acts as a co-activator with NRF2 to strengthen *de novo* GSH synthesis by upregulating GCLC expression, further suppressing ferroptosis in gastric cancer^[90]. Zinc finger MYND-type containing 8 (ZMYND8), a histone modification reader, interacts with NRF2 to enhance its transcriptional activity and recruit it to the promoters of antioxidant genes, thereby protecting breast cancer stem cells from ferroptosis^[91]. Notably, some biosynthetic enzymes also exert nonenzymatic function by modulating the activity of NRF2. Biliverdin reductase A (BVRA), the terminal enzyme in heme catabolism, moonlights as a transcription factor to cooperate with NRF2 to modulate the NRF2 transcriptional program^[92]. Moreover, TP53 induced glycolysis and apoptosis regulator (TIGAR), a regulator of glycolysis and apoptosis, binds to NRF2 and facilitates its nuclear translocation to confer chemotherapy resistance by maintaining redox balance^[93]. Thus, chromatin-associated proteins activate NRF2 transcriptional activity by recruiting NRF2 or modulating core histone modifications.

Besides mutual recruitment between NRF2 and co-factors, some chromatin-associated proteins function as chromatin organizers for NRF2 transcription. Special AT-rich binding protein-2 (SATB2) co-localizes with NRF2 to drive enhancer-promoter interactions and recruits SWI/SNF complex. This coordination between SATB2 and NRF2 enhances NRF2 transcriptional activity, amplifying resistance to oxidative stress in renal cell carcinoma^[94]. Moreover, deficiency of double PHD fingers 2 (DPF2), subunit of the canonical SWI/SNF complex, leads to the displacement of the catalytic subunit brahma-related gene 1 (BRG1) from NRF2-occupied enhancers, decreasing the expression of anti-inflammatory and antioxidant genes in hematopoietic stem cells^[95]. However, BRG1 may exert divergent or opposing roles in NRF2 signaling depending on tissue context, BRG1 expression status, or mutation frequency. For instance, BRG1 knockdown leads to increased NRF2 binding specifically at the *HMOX1* promoter, but not at other targets in NSCLC^[96]. Conversely, Yamamoto *et al.* demonstrated that NRF2-mediated *HMOX1* expression is BRG1-dependent in colorectal carcinoma cells (CRC)^[97].

Beyond co-activators, transcription factors can also function as suppressors of NRF2 activity. The tumor suppressor alternative reading frame (ARF) inhibits NRF2 transcription potential by directly binding to NRF2, thereby sensitizing cancer cells to ferroptosis in both p53-independent and p53-dependent manners^[98]. Moreover, nuclear receptors, whose conformation is altered by ligand binding, have been identified as negative regulators of the NRF2-ARE pathway. For example, upon glucocorticoids stimulation, the glucocorticoid receptor (GR) binds to NRF2 and is recruited to ARES. This interaction represses NRF2 transcriptional activity by reducing NRF2-dependent histone acetylation mediated by cAMP responsive element binding protein binding protein (CBP), a mechanism that may underlie certain side effects of glucocorticoids therapy^[99].

Additionally, several regulators modulate NRF2 activation by physically restricting its nuclear translocation (Figure 4). Tribbles homolog 1 (TRIB1) interacts with NRF2 to block its nuclear entry, thereby inhibiting target gene expression and restraining liver cell proliferation^[100]. Similarly, FCH and double SH3 domains 1 (FCHSD1) forms a cytosolic complex with NRF2 and sorting nexin 9 (SNX9), preventing NRF2 nuclear translocation and promoting the initiation of emphysema^[101].

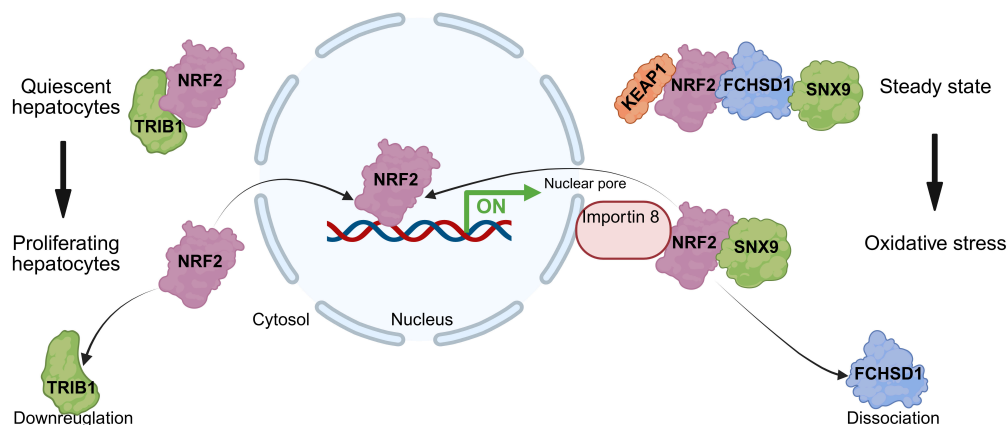


Figure 4. Regulators restricting NRF2 nuclear translocation. Schematic depicting proteins that interact with NRF2 in the cytoplasm to inhibit its nuclear entry. Regulators such as TRIB1 and FCHSD1 bind to NRF2, thereby sequestering it in the cytosol or preventing its translocation to the nucleus, consequently suppressing NRF2-mediated transcriptional activation under oxidative stress. Created in [BioRender.com](https://www.biorender.com). NRF2: nuclear factor erythroid 2-related factor 2; TRIB1: tribbles homolog 1; FCHSD1: FCH and double SH3 domains; SNX9: sorting nexin 9.

In summary, the transcriptional output of NRF2 is finely tuned by a complex network of chromatin remodelers, suppressive transcription factors, and translocation modulators, highlighting the context-dependent nature of NRF2 regulation in cancer progression and therapy response.

7. The Post Translational Modifications (PTMs) in NRF2 Regulation

Protein stability and nuclear accumulation of NRF2 are dynamically regulated by post-translational modifications, including acetylation, phosphorylation, ubiquitination, and methylation^[102]. Evaluating these processes across various cancer types is crucial for determining their impact on NRF2 transcriptional activity (Figure 5).

7.1 De/ubiquitination

Under basal conditions, the KEAP1-CUL3 E3 ubiquitin ligase complex targets NRF2 for cytoplasmic degradation. Recently, Ingersoll *et al.* identified thyroid hormone receptor interactor protein 12 (TRIP12) as a ubiquitin chain elongation factor within the KEAP1-CUL3 complex, dynamically controlling NRF2 degradation in response to ROS^[103]. In a KEAP1-independent manner, β -transducin repeat-containing protein (β -TrCP) associates with Cullin-1 (CUL1) and S-phase kinase-associated protein 1 (SKP1) to form an E3 ligase complex that targets nuclear NRF2 for proteasomal degradation^[104]. The distinction between KEAP1- and β -TrCP-mediated degradation likely reflects tissue-specific effects and subcellular compartmentalization^[105].

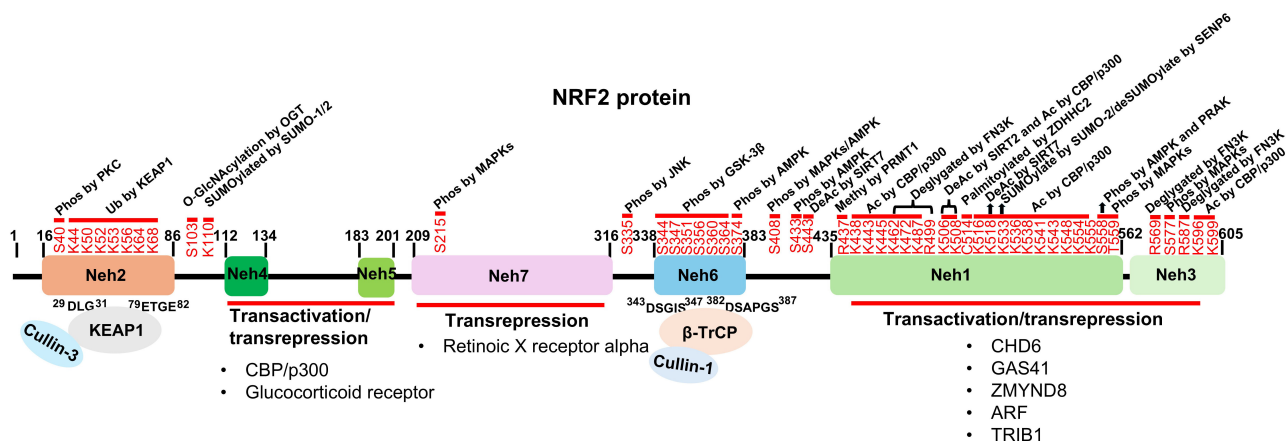


Figure 5. The PTMs, transactivation and domain-specific interactions regulating NRF2 stability and activity. Schematic map of NRF2 protein domains (Neh1–Neh6) highlighting key PTMs and binding partners. The Neh4, Neh5, Neh1, and Neh3 domains serve as docking sites for co-factors that either activate or suppress NRF2 transcriptional activity. Ubiquitination: KEAP1 and β -TrCP target the Neh2 and Neh6 domains, respectively, to mediate ubiquitination and proteasomal degradation; Acetylation: CBP/p300 mediates acetylation at multiple lysine residues within the Neh1 and Neh3 domains (K438, K443, K445, K462, K472, K487, K506, K508, K516, K518, K533, K536, K538, K541, K543, K548, K554, K555, K596, and K599), while SIRT2 deacetylates specific sites (K506, K508) and SIRT7 deacetylates sites (K443 and K518); Methylation: PRMT1 methylates NRF2 at arginine residue R437; Phosphorylation: Various kinases phosphorylate NRF2 at distinct sites to regulate its function, including PKC (S40), MAPKs (S215, S408, S558, T559, and S577), AMPK (S374, S408, S433, and S558), PRAK (S558), JNK (S335), and GSK-3 β (S344, S347, S351, S356, S360, and S364); Other PTMs: SUMOylation by SUMO-1/2 occurs at K110 and K533. FN3K mediates deglycation at multiple sites including K462, K472, K487, R499, R569, and R587. NRF2 is palmitoylated by ZDHHC2 at C514 and O-GlcNAcylated at S103. Neh: NRF2-ECH homology; NRF2: nuclear factor erythroid 2-related factor 2; PTMs: post translational modifications; KEAP1: Kelch-like ECH-associated protein 1; β -TrCP: β -transducin repeat-containing protein; CBP: cAMP responsive element binding protein binding protein; SIRT2: sirtuin 2; PRMT1: protein arginine methyltransferase 1; MAPKs: mitogen-activated protein kinases; PKC: protein kinase C; AMPK: adenosine 5'-monophosphate (AMP)-activated protein kinase; JNK: c-Jun NH₂-terminal kinase; PRAK: p38 regulated/activated protein kinase; GSK-3 β : glycogen synthase kinase 3 beta; FN3K: fructosamine 3 kinase; ZDHHC2: zinc finger DHHC-type containing 2; K: lysine; R: arginine; S: serine; C: cysteine; T: threonine.

Given the critical role of KEAP1 and β -TrCP in NRF2 stability, numerous proteins impair the KEAP1-NRF2 interaction to modulate redox homeostasis. Many proteins promote the dissociation of NRF2 from the KEAP1-CUL3 complex, allowing NRF2 to evade degradation. This stabilization supports tumor growth by preventing ferroptosis^[106–124]. Similarly, growth differentiation factor 15 (GDF15), peptidyl-prolyl cis-trans isomerase NIMA-interacting 1 (PIN1), peptidylprolyl isomerase A (PPIA), and HECT domain and ankyrin repeat containing E3 ubiquitin protein ligase 1 (HACE1) directly interact with NRF2, competing with KEAP1 binding and compromising NRF2 ubiquitination^[125–128]. Circular RNA produced by β -TrCP encodes a novel β -TrCP isoform, which competitively binds to NRF2 and blocks β -TrCP-mediated degradation^[129]. These mechanisms enhance NRF2 transcriptional activity, favoring cancer progression and radioresistance. Consequently, the overexpression of these competitive inhibitors can lead to constitutive NRF2 activation.

Besides KEAP1 and β -TrCP, one study demonstrates that mind bomb 1 (MIB1) overexpression sensitizes lung cancer cells to ferroptosis by inducing NRF2 proteasomal degradation^[130]. Meanwhile, STAM binding protein-like 1 (STAMBPL1) stabilizes NRF2 through K63 deubiquitination, thereby impeding ferroptosis and cholangiocarcinoma (CCA) progression^[131]. However, deubiquitination can also reverse this process. Deubiquitinase 3 (DUB3) promotes NRF2 activation and transcriptional activity, conferring chemotherapy resistance in colon cancer^[132]. Additionally, ubiquitin specific peptidase 11 (USP11) stabilizes NRF2 via deubiquitination, contributing to ferroptosis resistance and cell growth in NSCLC^[133]. In KRAS-mutated LUAD, ubiquitin specific peptidase 13 (USP13) catalyzes NRF2 deubiquitination, facilitating a switch from autophagy to ferroptosis resistance, thereby promoting tumor progression^[134]. While the proteasome is the primary degradation machinery, alternative pathways exist. Activation of transient receptor potential ankyrin 1 (TRPA1), a receptor potential ion channel, promotes the trafficking of NRF2 to lysosomes for degradation, a process independent of the canonical ubiquitin-proteasome system^[135]. Collectively, these precise regulator mechanisms govern NRF2 stability, where the disruption of this equilibrium by competing proteins or specific enzymes serves as a pivotal switch in determining tumor cell susceptibility to ferroptosis.

7.2 Sumoylation

Sumoylation involves the covalent attachment of Small Ubiquitin-like Modifier (SUMO) proteins to specific lysine residues on target proteins. NRF2 can be modified by SUMO-1 and SUMO-2/3, with SUMO-2/3 being the predominant modifiers^[136,137]. SUMO-1 modification at lysine 110 of NRF2 has been shown to sustain hepatocellular carcinoma cell growth^[138]. Meanwhile, SUMO-2-mediated sumoylation at lysine 110 and lysine 533 promotes NRF2 nuclear localization and transcriptional activity^[139]. Conversely,

Sentrin/SUMO-specific protease 6 (SENP6) acts as a negative regulator; by desumoylating NRF2, SENP6 enhances NRF2 ubiquitination and degradation, thereby inducing oxidative stress^[137].

7.3 De/acetylation

NRF2 acetylation by histone acetyltransferases (HATs) p300/CBP is essential for its transcriptional response to oxidative stress, augmenting DNA-binding activity in a promoter-specific manner^[88]. Additionally, Lysine acetyltransferase 8 (MOF)-mediated acetylation increases NRF2 nuclear retention and downstream gene transcription, regulating anti-drug responses in NSCLC^[140]. Conversely, Sirtuins, NAD-dependent deacetylases (HDACs), deacetylate NRF2, leading to either nuclear export or altered stability, thereby modulating antioxidant gene expression^[141-146]. HATs and deacetylases not only modify NRF2 directly but also act as co-factors to regulate chromatin accessibility and recruit the basal RNA polymerase machinery.

7.4 Methylation

Protein arginine methyltransferase 1 (PRMT1) is implicated as a co-activator within the p300/CBP complex. Liu *et al.* discovered that PRMT1 methylates NRF2 at arginine 437. This methylation enhances NRF2 DNA-binding and transcriptional activity, protecting cells against ROS-induced ferroptosis^[147]. In contrast, PRMT4 overexpression in doxorubicin-induced cardiomyopathy promotes ferroptosis by methylating NRF2 in a manner that restricts its nuclear translocation and suppresses GPX4 expression^[148].

7.5 Phosphorylation

Phosphorylation plays a vital role in regulating the subcellular distribution and activity of NRF2. Kinases such as casein kinase 2 (CK2), mitogen-activated protein kinases (MAPKs), protein kinase C (PKC), PKR-like endoplasmic reticulum kinase (PERK), and c-Jun NH₂-terminal kinase (JNK) are required for NRF2 nuclear translocation or degradation to maintain redox balance^[149-155]. However, p38 regulated/activated protein kinase (PRAK) phosphorylates NRF2 Serine 558, stabilizing NRF2 protein independent of ubiquitination to maintain redox homeostasis and the antitumor effects of T helper 17 cells^[156]. Notably, in tumor-associated myeloid-derived suppressor cells (MDSCs), PERK deficiency activates CD8⁺ T cell-mediated anti-tumor immunity by restricting NRF2 signaling. This leads to cytosolic mitochondrial DNA accumulation and subsequent type I interferon (IFN) production via the STING pathway^[157]. Since phosphoinositide 3-kinase/serine/threonine kinase (PI3K/AKT) inhibition restrains NRF2 phosphorylation, it represents a potential preclinical strategy to target therapy-resistant tumors^[158].

Adenosine 5'-monophosphate (AMP)-activated protein kinase (AMPK)-mediated phosphorylation of NRF2 yields site-specific effects. Phosphorylation at Serine 558 by AMPK accelerates NRF2 nuclear accumulation^[159]. Interestingly, AMPK also phosphorylates NRF2 at Serine 374, Serine 408, and Serine 433, which affects the transactivation of specific target genes without altering NRF2 protein levels or nuclear accumulation^[160]. Conversely, protein phosphatase 1 (PP1) dephosphorylates NRF2, promoting its nuclear export and enhancing tumor cell sensitivity to ferroptosis^[161]. Collectively, the phosphorylation landscape of NRF2 is highly complex and site-specific, serving as a convergence point for various signaling pathways to integrate environmental cues and dictate cell fate decisions.

7.6 Other PTM

Apart from classical modifications, NRF2 is regulated by a complex array of PTMs that drive malignancy. Glutarylation of NRF2 has been shown to increase its stability and DNA-binding activity, thereby modulating cell viability and promoting tumor growth^[162]. Similarly, Fructosamine-3-kinase (FN3K)-mediated deglycation is essential for NRF2 transcriptional competence, acting as a catalyst for NRF2-driven tumorigenesis^[163]. Nuclear retention and stability are further orchestrated by PARYlation and O-GlcNAcylation: PARP2-mediated PARYlation retains NRF2 in the nucleus to sustain antioxidant gene expression^[164], while O-GlcNAcylation at Serine 103 disrupts KEAP1-dependent ubiquitination, promoting nuclear accumulation and cancer malignancy^[165]. Finally, palmitoylation at Cysteine 514 protects NRF2 from proteasomal degradation, and its interruption significantly suppresses tumor development^[166].

8. Association of NRF2 with Core Histone Modifications

As noted, NRF2 cooperates with chromatin-binding proteins to alter chromatin conformation and recruit transcriptional machinery. This indicates that histone status is integral to NRF2 regulation. Conversely, histone modifications can be directly regulated by NRF2. For instance, the linker histone variant H1.2 interacts with NRF2 to promote its nuclear accumulation, while NRF2 transcriptionally upregulates H1.2. This H1.2-NRF2 feedforward loop drives tumor progression in NSCLC^[167].

Metabolic intermediates also link NRF2 to epigenetics. In the HCC mouse model, NRF2 ablation impairs metabolic pathways, reducing acetyl-CoA generation and suppressing histone acetylation in tumors (but not in normal tissue), thereby disrupting transcription complex assembly at antioxidant genes^[168]. Furthermore, 2-oxoglutarate (2OG), a cofactor for JmJc domain-containing histone demethylases, is regulated by NRF2 via the metabolic enzyme L-2-hydroxyglutarate dehydrogenase (L2HGDH)^[169,170]. NRF2-mediated production of 2OG affects histone methylation and modulates the ROS-induced ferroptosis response. Therefore, a bidirectional regulatory axis exists between NRF2 and the epigenetic landscape, mediated by direct protein interactions and metabolic signaling, which coordinates the sustained antioxidant program required for tumorigenesis.

9. Clinical Applications of NRF2 Inhibitors Induced-Ferroptosis for Cancer Therapy

NRF2 is the master regulator of the antioxidant response, and its role in cancer initiation and progression is well-established^[20]. However, the function of NRF2 in oncology is Janus-faced. While NRF2 inducers are desirable for suppressing early-stage carcinogenesis by alleviating inflammation and oxidative stress, constitutive NRF2 activation in malignant cells protects against ROS-induced ferroptosis. This promotes aggressive growth and metastasis, a phenomenon termed the “dark side” of NRF2^[171]. Consequently, targeting the NRF2-ferroptosis axis represents a promising pharmacological vulnerability in advanced cancer.

Although numerous NRF2 inhibitors have shown tumor-suppressive effects, few have successfully progressed through the drug development pipeline. A major hurdle is the intrinsically disordered nature of the NRF2 protein and its lack of druggable binding pockets. However, the convergence of drug repurposing strategies and cutting-edge Proteolysis-Targeting Chimeras (PROTAC) technology expands the horizon of NRF2-targeted therapies, promising to overcome the “undruggable” nature of NRF2 and deliver effective ferroptosis-inducing treatments to the clinic (Table 1).

Table 1. Inhibitors targeting NRF2 are listed with their mechanisms, efficacy in preclinical models, and supporting references.

Drug	Mechanism of action	Cancer types	Functions in ferroptosis	Reference
PZM	Decrease NRF2 transcriptional activity	ESCC	Increase ferroptosis sensitivity	[189]
AEM1	Decrease NRF2 transcriptional activity	NSCLC	Not reported	[185]
ML385	Decrease NRF2 transcriptional activity	AML; CRC	Increase ferroptosis sensitivity	[186,187]
ARE-PROTAC	Decrease NRF2 transcriptional activity	NSCLC	Increase ferroptosis sensitivity	[197]
CR-1-31B	Block NRF2 translation	Osteosarcoma	Not reported	[188]
Clobetasol propionate	Inhibit nuclear translocation of NRF2	NSCLC	Increase ferroptosis sensitivity	[192]
triptolide	Inhibit nuclear translocation of NRF2	NSCLC; Leukemia	Increase ferroptosis sensitivity	[178,179]
Trigonelline	Inhibit nuclear translocation of NRF2	HNC; NSCLC	Increase ferroptosis sensitivity	[176,177]
Sirolimus	Inhibit nuclear translocation of NRF2	SCC	Not reported	[191]
Brusatol	Enhanced NRF2 ubiquitination	NSCLC; EAC	Increase ferroptosis sensitivity	[173,175]
VVD-065	Enhanced NRF2 ubiquitination	NSCLC; ESCC; HNSCC	No reported	[182]
R16	Enhanced NRF2 ubiquitination	NSCLC	Not reported	[183]
CX-5461	Enhanced NRF2 ubiquitination	CRC	Increase ferroptosis sensitivity	[190]
Pyrimethamine	Enhanced NRF2 ubiquitination	ESCC; NSCLC	Not reported	[193,194]
ZVI-NP	Enhanced NRF2 ubiquitination or transcriptional repress NRF2 expression	NSCLC; ESCC	Increase ferroptosis sensitivity	[62,184]
2-(3-methylbenzyl) succinic acid	Restrain NRF2 activation	Melanoma; PDAC	Increase ferroptosis sensitivity	[180]

NRF2: nuclear factor erythroid 2-related factor 2; PZM: pizotifen malate; ESCC: esophageal squamous cell carcinoma; NSCLC: non-small cell lung cancer; CRC: colorectal carcinoma cells; HNSCC: head and neck squamous cell carcinoma; ZVI-NP: zero-valent-iron nanoparticle; ESCC: esophageal squamous cell carcinoma; HNC: head and neck cancer; SCC: squamous cell carcinoma; EAC: esophageal adenocarcinoma; AML: acute myeloid leukemia; PDAC: pancreatic ductal adenocarcinoma.

9.1 Natural compounds

Brusatol, a natural product, was the first identified potent NRF2 inhibitor that enhances NRF2 ubiquitination and degradation to combat chemoresistance^[172]. Combining brusatol with ferroptosis inducers sensitizes cancer cells to death, offering a potential therapeutic strategy^[173-175]. Trigonelline reduces NRF2 nuclear accumulation via epidermal growth factor receptor (EGFR) signaling and cooperates with ferroptosis inducers to restore chemosensitivity^[176,177]. Similarly, Triptolide inhibits NRF2 downstream targets by affecting nuclear localization and exerts robust synergistic effects with ferroptosis inducers^[178,179]. Furthermore, targeting the tumor microenvironment (TME) reveals that the itaconate transporter SLC13A3 endows tumors with ferroptosis resistance via the NRF2-SLC7A11 pathway^[180,181]. Inhibiting SLC13A3 by 2-(3-methylbenzyl) succinic acid sensitizes cells to ferroptotic stress and enhances tumor immunity.

9.2 Synthetic inhibitors

VVD-065 is a first-in-class covalent inhibitor that engages Cysteine151 on KEAP1 to induce KEAP1-CUL3 complex formation, enhancing NRF2 degradation and suppressing tumor growth^[182]. Meanwhile, R16 selectively binds KEAP1 mutants to restore the NRF2 and KEAP1 interaction, downregulating NRF2 and reducing chemoresistance in KEAP1-mutant tumor cells^[183]. Although the direct impact of VVD-065 and R16 on ferroptosis remains to be fully elucidated, they hold significant potential for treating cancers with KEAP1 somatic mutations. Meanwhile, zero-valent-iron nanoparticle (ZVI-NP) can induce cancer-specific cytotoxicity and anti-cancer immunity. Mechanically, ZVI-NP inhibits NRF2 expression by enhancing β -TrCP-dependent degradation or recovering SOX17/NRF2 axis to induce lung cancer ferroptosis and tumor growth^[62,184]. Additionally, synthetic compounds like ML385 and AEM1 decrease NRF2 transcriptional activity and show promise in ferroptosis-based therapy^[185-187]. Beyond transcriptional control, eukaryotic translation initiation factor 4A1 (EIF4A1) inhibitors like CR-1-31B and the clinical-grade eFT226 (NCT04092673) block NRF2 translation, reducing metastatic burden^[188].

9.3 Drug repurposing

Drug repurposing offers an efficient route to identify NRF2 inhibitors. Pizotifen malate (PZM), an FDA-approved medication, binds to the Neh1 domain of NRF2 and prevents NRF2 protein binding to the ARE motif of target genes, suppressing the transcriptional activity of NRF2 to induce ferroptosis and inhibit tumor growth^[189]. CX-5461, an RNA polymerase I inhibitor approved for breast cancer susceptibility gene 1/2 (BRCA1/2)-mutant cancers, promotes NRF2 ubiquitination and induces ferroptosis in colorectal cancer^[190]. Sirolimus (Rapamycin), an mTORC1 inhibitor and immunosuppressant, suppresses NRF2 expression and nuclear localization, restraining tumor growth in kidney transplant patients^[191]. Clobetasol propionate (CP), a corticosteroid, enhances radiosensitization by inhibiting NRF2 nuclear translocation and inducing ferroptosis^[192]. Pyrimethamine (PYR), an anti-parasitic drug, acts as a signal transducer and activator of transcription 3 (STAT3) inhibitor and has shown indirect NRF2 inhibitory activity by promoting ubiquitination^[193,194]. PYR and its derivative WCDD115 effectively suppress NRF2-driven cancers, with clinical trials in head and neck squamous cell carcinoma already completed (NCT05678348). These repurposed drugs hold immediate translational value for oncology.

9.4 PROTAC technology

Given the difficulties in developing direct NRF2 inhibitors, PROTACs offer an alternative by eliminating the target protein^[195]. A recently published PROTAC NRF2 degrader demonstrates anti-cancer effects in cells with constitutive NRF2 activation^[196]. Furthermore, Ji *et al.* reported an ARE-PROTAC that degrades NRF2-MAFG heterodimers via ubiquitination, sensitizing NSCLC cells to ferroptosis^[197]. However, the clinical translation of NRF2-targeting PROTACs requires overcoming challenges related to off-target effects and drug delivery.

10. Conclusion and Future Perspective

In conclusion, the NRF2-KEAP1 signaling axis acts as a pivotal guardian of cellular redox homeostasis and tumorigenesis. While NRF2 provides cytoprotection in normal physiology, its constitutive activation, driven by somatic mutations in *NFE2L2/KEAP1*, oncogenic signaling, and epigenetic rewiring, is frequently hijacked by advanced malignancies to circumvent oxidative stress and suppress ferroptosis. As highlighted in this review, the regulation of NRF2 extends far beyond the canonical KEAP1-dependent degradation machinery. A complex regulatory network, comprising epigenetic modifiers, non-coding RNAs, and chromatin-associated co-factors, orchestrates the fine-tuning of NRF2 transcriptional output. This intricate interplay confers robustness to cancer cells, enabling metabolic adaptability and resistance to ferroptosis-inducing therapies.

Looking forward, several critical avenues warrant further investigation to translate these mechanistic insights into clinical benefits. First, given the “undruggable” structural nature of NRF2 itself, targeting the distinct upstream regulators and co-factors identified herein offers a promising alternative. Moreover, identification of the undescribed downstream targets of NRF2 may also provide additional paths to kill tumors by triggering ferroptosis. Second, as current biomarkers for monitoring ferroptosis *in vivo* remain elusive, the identification of reliable signatures reflecting NRF2-dependent ferroptosis resistance will be instrumental in stratifying patients who are most likely to benefit from NRF2-targeted interventions. Ultimately, unraveling the multi-layered regulation of the

NRF2-ferroptosis axis holds the potential to unlock novel therapeutic vulnerabilities in refractory cancers.

Declarations

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Author contribution

Wang Z: Conceptualization, manuscript writing-original draft, and writing-reviewing.

Geng Z: Manuscript writing-original draft.

Gu W: Writing-reviewing.

Conflicts of interest

All authors declare no conflicts of interest.

Ethical approval

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Consent to participate

Not applicable.

Consent for publication

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