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NRF2'nin Kanserde Stres Odaklı Sinyalleşme ve Metabolik Yeniden Programlamadaki Rolü

The Role of NRF2 in Stress-Driven Signaling and Metabolic Reprogramming in Cancer

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Özet

Tümör hücreleri, hipoksi, oksidatif stres ve terapötik etkiler gibi çevresel streslere yanıt olarak enerji metabolizmalarını yeniden programlama yeteneği kazanır. Bu adaptif değişimi yönlendiren temel faktörler arasında, redoks homeostazı ve ara metabolizmanın ana transkripsiyonel düzenleyicisi olan Nrf2 ve ilişkili sinyal yolu aktivasyonları yer almaktadır. Nrf2'nin glikoliz, lipit metabolizması ve amino asit dönüşümünü düzenlemede rol oynadığı ve bunların her birinin ilaç direncinin ortaya çıkmasına ve sürdürülmesine de katkıda bulunduğu bilinmektedir. Aktive Nrf2, glutatyon biyosentezi, NADPH rejenerasyonu ve ksenobiyotik metabolizmasında rol oynayan sitoprotektif genlerin promotörlerindeki ARE'lere bağlanarak gerek tümör ilerlemesini, gerekse de p53 birikimini destekleyerek hücre ölümünü başlatabilir. Antioksidan savunma ve detoksifikasyonda rol oynayan genlerin transkripsiyonel aktivasyonu yoluyla Nrf2, kanser hücrelerini oksidatif hasardan ve kemoterapötik etkilerden korur. Nrf2 glikasyon yollarını hedeflemek, pro-oksidan tedavilerin etkinliğini arttırmada ve tümör antioksidan savunmalarını zayıflatmada bir strateji olarak önemlidir. Tüm bu transkripsiyonel yeniden programlamalar, ROS'un detoksifikasyonunu, redoks homeostazının restorasyonunu ve oksidatif lezyonların onarımını kolaylaştırarak hücresel sağkalımı destekler. Bazal koşullar altında, Nrf2 sitoplazmada Keap1 tarafından ubikitinlenir ve parçalanır. Tümörigenezde onkometabolit birikiminden kaynaklanan artan ROS seviyeleri, Keap1 üzerindeki sistein kalıntılarını değiştirerek, Nrf2'yi parçalanmak üzere hedefleme yeteneğini zayıflatır. Bu durum, Nrf2'nin çekirdeğe taşınmasına ve burada ARE tarafından yönlendirilen genlerin transkripsiyonunu aktive ederek hücresel antioksidan kapasitesini artırmasına ve oksidatif stres altında hayatta kalmayı desteklemesine olanak tanır. NRF2'nin kanserde bahsedilen tüm bu yeniden programlama süreçleri, özellikle glikoliz, glutaminoliz ve redoks tamponlaması, kanser hücrelerinde anabolik büyümeyi içeren metabolik reprogramlanmayı ve stres adaptasyonunu desteklemesi açısından kritik öneme sahiptir.

Anahtar Kelimeler: Nrf2, stres, metabolik yeniden programlama, kanser, terapötik direnç

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Abstract

Tumor cells acquire the ability to reprogram their energy metabolism in response to environmental stresses such as hypoxia, oxidative stress, and therapeutic effects. Key factors driving this adaptive shift include Nrf2, a master transcriptional regulator of redox homeostasis and intermediary metabolism, and activation of associated signaling pathways. Nrf2 is known to play a role in regulating glycolysis, lipid metabolism, and amino acid turnover, each of which contributes to the emergence and maintenance of drug resistance. Activated Nrf2 can bind to AREs in the promoters of cytoprotective genes involved in glutathione biosynthesis, NADPH regeneration, and xenobiotic metabolism, thereby promoting both tumor progression and cell death by promoting p53 accumulation. Through transcriptional activation of genes involved in antioxidant defense and detoxification, Nrf2 protects cancer cells from oxidative damage and chemotherapeutic effects. Targeting Nrf2 glycation pathways is important as a strategy to enhance the efficacy of pro-oxidant therapies and weaken tumor antioxidant defenses. All of these transcriptional reprogrammings promote cellular survival by facilitating the detoxification of ROS, restoration of redox homeostasis, and repair of oxidative lesions. Under basal conditions, Nrf2 is ubiquitinated and degraded in the cytoplasm by Keap1. Increased ROS levels resulting from oncometabolite accumulation in tumorigenesis modify cysteine residues on Keap1, weakening its ability to target Nrf2 for degradation. This allows Nrf2 to translocate to the nucleus, where it activates the transcription of ARE-driven genes, enhancing cellular antioxidant capacity and supporting survival under oxidative stress. All of these reprogramming processes mentioned by NRF2 in cancer, particularly glycolysis, glutaminolysis, and redox buffering, are critical for supporting metabolic reprogramming and stress adaptation, including anabolic growth in cancer cells.

Keywords: NRF2, stress, metabolic reprogramming, cancer, therapeutic resistance

Introduction

Nrf2, encoded by Nfe2l2, is a master transcriptional regulator that orchestrates the cellular defense program against oxidative and electrophilic stress by coordinating a broad gene network responsible for redox homeostasis, phase II detoxification, xenobiotic metabolism, and cytoprotection (1, 2). Through selective binding to the antioxidant response element (ARE), a conserved cis-regulatory motif, Nrf2 governs the transcription of multiple defense genes—including GCL, Txnrd1, NQO1, and HMOX1—thereby establishing a core mechanism for redox-sensitive gene regulation (3). Beyond its canonical role in redox control, accumulating evidence indicates that NRF2 is embedded within broader oncogenic signaling circuits, including the PI3K/AKT axis, pro-inflammatory NF-κB pathways, and developmental programs such as Hedgehog signaling, which are frequently deregulated in gastrointestinal malignancies (4).

Nrf2 is a member of the Cap ‘n’ Collar (CNC) basic leucine zipper (bZIP) transcription factor family, alongside Nrf1 and Nrf3, which collectively shape cellular redox and metabolic adaptation (5). This family also includes the transcriptional repressors Bach1 and Bach2, which antagonize Nrf2 by competitively binding ARE sequences under homeostatic conditions, thereby constraining cytoprotective gene expression (5, 6). Structurally, Nrf2 harbors a CNC motif and seven Nrf2-ECH homology domains that regulate transcriptional activity, protein stability, and cofactor binding (7). Central to its degradation

is the N-terminal Neh2 domain, which enables high-affinity interaction with Kelch-like ECH–associated protein 1 (Keap1), a cysteine-rich adaptor protein tethered to the actin cytoskeleton. Keap1 recruits Nrf2 to the Cullin-3 (Cul3) E3 ubiquitin–ligase complex, promoting constitutive ubiquitination and proteasomal degradation, thereby maintaining low basal Nrf2 activity and tight repression of ARE-dependent transcription (8).

Metabolic rewiring is a hallmark of tumor progression, particularly in digestive system cancers where hypoxia, inflammation, and nutrient fluctuations impose strong selective pressures. Nrf2 has emerged as a major regulator of this adaptive interface by modulating glycolysis, glutaminolysis, mitochondrial respiration, lipogenesis, and PPP flux (9). In gastric cancer, CHFR has been shown to promote epithelial–mesenchymal transition and metastatic dissemination by activating AKT and ERK signaling through an NRF2-dependent increase in reactive oxygen species, thereby linking oncogenic kinase cascades to the NRF2 redox program in vivo and in vitro (4). In colorectal cancer, enforced Nrf2 overexpression augments AKT and ERK phosphorylation, accelerates tumor growth, and enhances invasive behavior, whereas Nrf2 knockdown reverses these phenotypes and reduces xenograft burden(10). These data collectively position NRF2 both upstream and downstream of PI3K/AKT signaling modules that drive growth and survival in GI tumors.

Classical and contemporary studies demonstrate that Nrf2 enhances NADPH generation, supports glutathione biosynthesis, and preserves thiol redox balance—functions that collectively sustain survival under oxidative or therapeutic stress (8,9). Recent multi-omics analyses and ^13C metabolic flux experiments further support a model in which Nrf2 rewires central carbon metabolism to maintain biosynthetic and antioxidant capacity during malignant progression (11).

Aerobic glycolysis (the Warburg effect) is one of the most extensively characterized metabolic adaptations in pancreatic ductal adenocarcinoma (PDAC), colorectal cancer (CRC), and gastric cancer (GC). Notably, ionizing radiation promotes strong Nrf2 activation in PDAC, leading to transcriptional upregulation of glycolytic enzymes, enhanced lactate output, and reinforcement of a pro-survival metabolic state (12, 13). Inhibition or knockdown of Nrf2 restores radiosensitivity in resistant PDAC models, demonstrating that Nrf2-dependent metabolic rewiring is a critical determinant of radiation tolerance (13, 14). Similar findings have been reported in CRC and HCC, suggesting a pan-GI metabolic phenotype in which Nrf2 sustains redox and bioenergetic fitness under stress (15, 16). It is important to mention that a major conceptual expansion in Nrf2 biology has emerged from the discovery of a glycation–deglycation regulatory axis. The seminal study demonstrated that Nrf2 undergoes spontaneous non-enzymatic glycation at lysine and arginine residues, which suppresses its transcriptional activity unless reversed by fructosamine-3-kinase (FN3K) (17).

Loss of FN3K impairs Nrf2 binding to ARE-containing promoters, markedly reduces transcription of canonical targets such as NQO1, TXNRD1, and GPX2, and diminishes cellular antioxidant capacity. Structural studies have further elucidated the mechanistic basis of FN3K activity. The crystal structure of human FN3K reveals a kinase-like fold containing conserved active-site motifs that mediate MgATP coordination and catalytic phosphorylation of Amadori-modified lysines (18). Biochemical assays corroborate that FN3K phosphorylates fructosyl-lysine adducts on NRF2 through an ordered catalytic mechanism, thereby enabling subsequent deglycation and restoration of transcriptional function (19). Complementary reviews propose FN3K inhibition as a therapeutic strategy to attenuate Nrf2 hyperactivation in cancer, highlighting its emerging translational relevance (20).

Beyond oxidative cues, Nrf2 is activated by amino-acid deprivation and ER stress through a conserved nutrient-sensing pathway involving GCN2, eIF2α, ATF4, and SESN2. Under amino-acid limitation, uncharged tRNAs activate GCN2, which phosphorylates eIF2α and induces ATF4 translation—a canonical component of the integrated stress response. ATF4 transcriptionally activates SESN2, which modulates mTORC1 via GATOR complexes and promotes Nrf2 activation indirectly by facilitating p62 phosphorylation and KEAP1 sequestration (21, 22). This GCN2→eIF2α→ATF4→SESN2 axis links

nutritional stress to non-canonical NRF2 stabilization, providing a mechanistic bridge between nutrient signaling and redox adaptation. In parallel, primary tumor models in diverse tissues indicate that NRF2 also engages in bidirectional crosstalk with NF-κB-driven inflammatory signaling and Hedgehog pathway components, suggesting that redox-responsive NRF2 circuits can intersect with canonical pro-inflammatory and developmental programs that are recurrently altered in gastrointestinal tumorigenesis.

This review aims to dissect the mechanistic roles of Nrf2 in regulating redox homeostasis, metabolic reprogramming, and adaptive stress responses in digestive system cancers, with a particular focus on its interplay with hypoxia signaling, metabolic pathways, and therapy resistance—thereby providing an integrative framework to guide biomarker development and targeted therapeutic strategies.

1- FN3K– Nrf2 Axis as a Master Regulator of Stress Signaling, Metabolic Plasticity, and Tumor Adaptation

Metabolic rewiring is increasingly recognized as a hallmark of malignant transformation and progression, particularly in digestive system cancers. Tumor cells acquire the capacity to reprogram intermediary metabolism in response to environmental pressures such as hypoxia, oxidative stress, nutrient deprivation, and therapeutic insults. Among the central players orchestrating this adaptive shift is Nrf2, a master transcriptional regulator of redox homeostasis and metabolic resilience (23). Mounting evidence implicates Nrf2in the modulation of glycolysis, lipid metabolism, and amino-acid turnover, three interconnected metabolic axes that support proliferation and the emergence of drug resistance in gastrointestinal malignancies (23, 24). Recent high-resolution omics studies have expanded this framework by showing that Nrf2coordinates multiple metabolic nodes simultaneously. For example, the research article demonstrated that Nrf2upregulates glycolytic and serine synthesis enzymes to support anabolic growth in tumor cells (24, 25). Similarly, it was also depicted that oncogenic KRAS and NRF2 cooperate to rewire central carbon metabolism, thereby enhancing antioxidant capacity in pancreatic ductal adenocarcinoma (26, 27). demonstrate that clinically approved KRAS-G12C inhibitors, including Sotorasib and Adagrasib, exert a dual mechanism of action that extends beyond mutant KRAS inhibition (26). They show that, at physiologically relevant concentrations, these inhibitors also activate the NRF2 pathway. This occurs because both compounds possess electrophilic warheads capable of covalently modifying KEAP1, the key negative regulator of Nrf2. Beyond canonical antioxidant signaling, it is also. reveal that KRAS-G12C inhibitors initiate a Nrf2-dependent secretory program (NISP) (26). It means that the treatment with these inhibitors increases expression and secretion of chemokines such as CCL2, CCL7, and CXCL5, but only in cells with a functional KEAP1–NRF2 pathway. These chemokines support immune-cell recruitment, and that NRF2 activation by G12C inhibitors contributes to enhanced anti-tumor immune surveillance (26, 28).

Complementing these findings, ^13C metabolic flux analysis (MFA)–based investigations have confirmed that NRF2 diverts glucose metabolites toward the pentose phosphate pathway and glutathione biosynthesis, reinforcing the cellular capacity to buffer redox stress and resist therapy (11, 12).

Indeed, increased reliance on aerobic glycolysis—commonly referred to as the Warburg effect—is a well-characterized metabolic adaptation in cancer cells, enabling rapid biomass synthesis and sustained ATP production even under hypoxic microenvironmental conditions. This metabolic shift not only fuels anabolic growth but also contributes substantially to therapeutic evasion. Recent studies in pancreatic ductal adenocarcinoma (PDAC) have identified NRF2 as a critical mediator of this glycolytic reprogramming (13). For instance, ionizing radiation induces robust Nrf2activation, which upregulates key glycolytic enzymes, enhances lactate production, and promotes a survival-favoring metabolic phenotype in PDAC cells (14). Notably, genetic or pharmacological inhibition of NRF2 re-sensitized resistant PDAC models to radiation, demonstrating its indispensable role in radioprotection (14, 29).

Additional mechanistic evidence from human PDAC models shows that Nrf2directly enhances glycolytic

flux through transcriptional activation of metabolic genes, including glucose transporter 1 (GLUT1) and phosphoglycerate dehydrogenase (PHGDH), thereby integrating Nrf2activity with broader metabolic remodeling beyond canonical antioxidant pathways (30). Furthermore, oncogenic KRAS—a defining driver of PDAC—was shown to promote Nrf2-dependent glucose carbon incorporation into serine biosynthesis and redox-supporting pathways, reinforcing Nrf2's position at the interface between metabolic plasticity and tumor survival (31).

Recent evidence has also uncovered a distinct post-translational regulatory mechanism in which Nrf2undergoes glycation, functioning as a metabolic rheostat that modulates its transcriptional competency under oncogenic stress. Specifically, Sanghvi et al. demonstrated that glycation of critical lysine and arginine residues—most notably K462, K472, and K487—impairs Nrf2's ability to regulate downstream antioxidant genes. This modification was verified using targeted liquid chromatography–tandem mass spectrometry (LC-MS/MS), which identified glycation adducts on Nrf2 with high specificity (17). Collectively, these findings highlight that both metabolic and glycation-dependent mechanisms converge upon NRF2 to support tumor fitness, therapy resistance, and redox integrity.

Functional inactivation of Nrf2 through glycation significantly diminishes the expression of canonical Nrf2 target genes such as NQO1, TXNRD1, and GPX2, as demonstrated by both immunoblotting and quantitative transcriptional analyses (17, 32). These findings underscore the centrality of post-translational modifications in dictating Nrf2 transcriptional competence. Beyond glycation, at least three major stress-responsive pathways converge on Nrf2 to modulate its activation status via distinct upstream sensors: (i) reactive oxygen species induce KEAP1 cysteine oxidation, thereby disrupting KEAP1-mediated ubiquitination; (ii) the glycation–deglycation cycle is regulated by FN3K, which restores Nrf2 activity by reversing Amadori adduct formation; and (iii) amino acid starvation triggers the GCN2→eIF2α→ATF4→SESN2 axis, which has been shown to promote NRF2 activation through p62 phosphorylation and subsequent modulation of the GATOR2–mTOR complex (Table1) (20, 22, 33-35).

Moreover, chromatin immunoprecipitation (ChIP) assays revealed that Nrf2 binding to ARE sequences in the promoters of these antioxidant genes is markedly reduced in FN3K-deficient cells—the only known mammalian system in which fructosamine-3-kinase is absent—highlighting that deglycation is essential for preserving Nrf2–sMaf dimerization and DNA occupancy (17, 19). Complementary biochemical evidence shows that FN3K-dependent deglycation restores Nrf2's ability to engage AREs and reactivate redox-protective transcriptional programs after metabolic stress(20, 34). To sum up, these mechanistic insights position the FN3K– Nrf2 axis as a critical regulatory node that integrates oxidative, metabolic, and nutrient-derived signals into a unified transcriptional response.

Table 1. Cellular stress types and mechanisms regulating NRF2 activation

Signal Type	Sensor/Regulator	Downstream Impact
ROS/oxidants	Keap1 cysteine oxidation	Nrf2 stabilization
Glycation stress	FN3K → Nrf2 deglycation	Preserves NRF2–sMAF interaction
ER/AA stress	GCN2 → eIF2α → ATF4 → SESN2	Supports Nrf2 activation via p62 and GATOR2–mTOR axis

FN3K, Fructosamine-3-kinase; ROS, Reactive Oxygen Species; ER, Endoplasmic Reticulum; SESN2, Sestrin-2; NRF2, Nuclear factor erythroid 2–related factor 2; keap1, Kelch-Like ECH-Associated Protein 1 sMAF, small Maf proteins; GCN2, General control nonderepressible 2 kinase; eIF2α, eukaryotic initiation factor 2 alpha; ATF4, Activating transcription factor 4.

Experimental models of hepatocellular carcinoma receiving CRISPR-mediated co-deletion of Keap1 and Fn3k showed a striking reduction in tumor volume(35). In these dual-targeted models indicate that the inability to deglycate Nrf2 renders it transcriptionally inactive, thereby impairing tumor growth(17). Mechanistically, two primary effects underlie this tumor-suppressive phenotype: (1) glycation destabilizes Nrf2 and disrupts its interaction with essential co-factors, and (2) the consequent attenuation of antioxidant gene expression sensitizes cancer cells to oxidative damage.

Importantly, treatment with the antioxidant N-acetyl cysteine (NAC) partially restored Nrf2 target gene expression and intracellular glutathione levels, highlighting that redox homeostasis is tightly coupled to Nrf2's transcriptional competency(17, 36). These rescue experiments confirm that the observed phenotypes are indeed attributable to compromised Nrf2 activity rather than off-target effects of FN3K depletion. these findings reveal an unexpected layer of Nrf2 regulation through glycation and establish FN3K as a critical modulator of Nrf2 functionality in tumor cells. The loss of Nrf2's redox-protective functions in FN3K-deficient settings creates a metabolic vulnerability that can be therapeutically exploited, especially in oxidative stress-rich tumor microenvironments such as those found in hepatocellular and gastrointestinal cancers(37, 38). Another important part which is essential to shed light into it is that Nrf2 glycation has been shown to impede its interaction with essential partners, such as sMAF proteins, thereby affecting its role in cellular defense mechanism. This modification can lead to altered signaling outcomes, impacting the progression and treatment resistance of various cancers, including those of the digestive system and the lungs (22). It is important to mention that FN3K is an enzyme that mitigates the accumulation of advanced glycation end products (AGEs) by catalyzing the deglycation of fructosamines, thereby preserving protein function and cellular homeostasis(20, 34). Glycation alters protein structure and stability, compromising function; FN3K preserves proteostasis by enzymatically reversing these modifications, thereby maintaining protein activity. By preventing the accumulation and cross-linking of AGEs—which promote protein aggregation and generate reactive oxygen species (ROS)—FN3K indirectly mitigates oxidative stress and safeguards cellular integrity(34, 39).

Notably, the Neh1 domain, which encompasses the CNC-bZIP configuration, facilitates heterodimerization with members of the sMaf family—MafF, MafG, and MafK—thereby enabling DNA binding and transcriptional activation of target AREs (40, 41). Nrf2/sMaf heterodimers regulate the expression of target genes by binding to AREs or MAF recognition elements (MAREs). Indeed, This heterodimerization enables Nrf2 to bind to AREs/electrophile response elements (EpREs) within the promoters of phase II detoxifying genes, thereby enhancing their transcription, including that

of NFE2L2 itself(42, 43). It is also evidenced that activation of Nrf2 enhances cancer cell migration and invasion by upregulating the transcription factor BTB and CNC homology 1 (BACH1), thereby facilitating tumor progression(37, 44). Nrf2 may contribute to tumor malignancy by binding to AREs within the promoter regions of Notch1 and the p53 inhibitor Mdm2, the latter of which promotes p53 accumulation and ultimately induces cell death(45, 46).

This insight provides a compelling rationale for targeting NRF2 glycation pathways as a strategy for impairing tumor antioxidant defenses, the metabolic shifting as a background profound effects and enhancing the efficacy of pro-oxidant therapies.

2- Multilayered Upstream Modulators of Nrf2: p21, AKT–GSK3β Signaling, and Stress-Responsive Crosstalk in Tumor Adaptation

On the other hand, recent findings elucidate a noncanonical regulatory role of p21 in redox homeostasis through its direct interaction with Nrf2, a master transcription factor governing antioxidant defense(47). Mechanistically, p21 binds to the DLG and ETGE motifs of Nrf2 via its C-terminal KRR domain, competitively disrupting Keap1-mediated ubiquitination and thereby stabilizing Nrf2 protein levels(48, 49). This molecular interference prolongs Nrf2 half-life and enhances its transcriptional activity, as demonstrated by increased expression of canonical antioxidant genes, including NQO1 and HO-1(49). In cell-based models, p21-proficient (p21+/+) cells exhibited elevated basal and inducible Nrf2 activity, while p21-deficient cells showed impaired antioxidant responses(47, 50). These observations were corroborated in vivo, where p21-null mice displayed significantly reduced Nrf2 expression and diminished induction of downstream targets following oxidative challenge. Luciferase reporter assays and qRT-PCR analyses further confirmed that p21 overexpression augments Nrf2-driven transcription in a statistically significant manner Immunoprecipitation and ubiquitination assays provided molecular evidence of disrupted Keap1–Nrf2 interactions in the presence of p21, reinforcing the proposed mechanism. Collectively, these findings establish p21 as a critical modulator of the Keap1–Nrf2 axis, linking cell cycle regulation to oxidative stress resilience through post-translational stabilization of Nrf2(49).

Moreover, Nrf2 activation influences the expression of growth factors and downstream signaling pathways. In hepatocyte-specific Nrf2 activation models, there was a notable upregulation of growth factor genes, including those encoding for platelet-derived growth factor receptor (PDGFR) and epidermal growth factor receptor (EGFR), leading to enhanced AKT signaling. This was evidenced by increased phosphorylation levels of AKT and its downstream targets, correlating with hepatomegaly characterized by glycogen and lipid accumulation in the liver. These findings highlight Nrf2's role in modulating metabolic pathways and cellular proliferation through growth factor signaling cascades (51).

Nrf2 orchestrates a complex regulatory network involving the PI3K/AKT pathway, GSK-3β, p62/SQSTM1, insulin-like growth factor 1 (IGF-1), and hypoxia-inducible factor 1-alpha (HIF-1α), particularly in the context of digestive system cancers(52-54). Activation of the PI3K/AKT pathway leads to phosphorylation and inactivation of GSK-3β at serine 9, which prevents GSK-3β-mediated phosphorylation and subsequent β-TrCP–dependent degradation of Nrf2, thereby enhancing Nrf2 stability and nuclear translocation. For instance, in MCF-7 cells, IGF-1 stimulation increased AKT phosphorylation at S473 and GSK-3β phosphorylation at S9, effects that were attenuated by the PI3K inhibitor LY294002, underscoring the PI3K/AKT pathway's role in modulating Nrf2 activity. This mechanism operates independently of the canonical Keap1-mediated degradation pathway, as overexpression of Keap1 did not significantly impact IGF-1–induced Nrf2 activation(52).

Based on documented evidence which employed a robust, multi-faceted experimental design to elucidate the molecular mechanisms by which the Zn(II)-curcumin complex modulates cancer cell survival, with particular emphasis on the interplay between NRF2, p62, and p53 in the context of tumor progression. Using SKBR3 (breast cancer) and U373 (glioblastoma) cell lines—both expressing mutant p53 variants (R273H and R175H)—the conducted

Western blot analyses, revealing a significant upregulation of NRF2, p62, and HO-1 protein levels, accompanied by a notable reduction in Keap1 expression following Zn(II)-curc treatment. It has been suggested that the NRF2-p62 feedback loop contributes to chemoresistance by mitigating Keap1 suppression and interfering with p53-dependent apoptotic pathways, thereby promoting cancer cell survival under therapeutic stress (36,40).

Additionally, the interplay between Nrf2 and p62 is critical in regulating autophagy and oxidative stress responses. p62 can bind to keap1, facilitating Nrf2 release and activation(54). In DU145 cells, treatment with the GSK-3β inhibitor SB415286 led to increased levels of Nrf2 and its downstream target BNIP3, a protein involved in mitophagy, without affecting general autophagy markers like p62 and p-p70 S6 kinase(54, 55). These findings reveal that NRF2 functions as a mechanistic hub integrating diverse post translational signals with critical survival pathways. For example, glycation of NRF2 within the Neh1 DNA-binding domain,-specifically at Lys462, 472, and 487- impairs heterodimerization with sMAF factors and reduces ARE binding; mass spectrometry confirmed accumulation of Amadori adducts at these sites in keap1-mutant Huh1 cells, leading to diminished transcription of NQO1, TXNRD1, and GPX2 (17, 56-58). FN3K reverses this modification by phosphorylating the Amadori intermediate, restoring NRF2's ability to bind DNA and reinforcing transcriptional competence—highlighted by a dramatic ~87% reduction in tumor volume in Keap1/Fn3k double-knockout HCC models (17). In parallel, ubiquitination via the Keap1–Cul3–β-TrCP complex remains the classic degradative pathway; however, phosphorylation by GSK3β creates degron motifs that facilitate β TrCP–mediated ubiquitination. Since AKT phosphorylates and inhibits GSK3β, AKT-driven signaling fosters NRF2 stabilization—thereby linking growth pathways with redox resilience and presenting a rationale for dual targeting of AKT and NRF2 in tumors with hyperactive PI3K/AKT signaling(59, 60).

Moreover, competitive Keap1 binding by p21, p62, and PGAM5 disrupts the Keap1–Neh2 interface. For instance, p21 binds directly to NRF2's DLG and ETGE motifs, preventing Keap1 association and extending NRF2 half-life—evident in models showing elevated NQO1 and HO-1 levels and enhanced antioxidant responses in p21-proficient cells Concurrently, p62-mediated autophagic flux leads to Keap1 sequestration, activating NRF2 and promoting downstream mitophagic processes through BNIP3 upregulation; this highlights an autophagy-redox axis that sustains mitochondrial integrity under metabolic stress. These mechanistic insights elevate NRF2 beyond a simple stress sensor to a stress-integrative switch, regulated by metabolic signals (glycation), phosphorylation cascades (AKT–GSK3β), and protein–protein interactions (p21, p62), each converging on its stabilization and transcriptional activity (61, 62) (Figure 1).

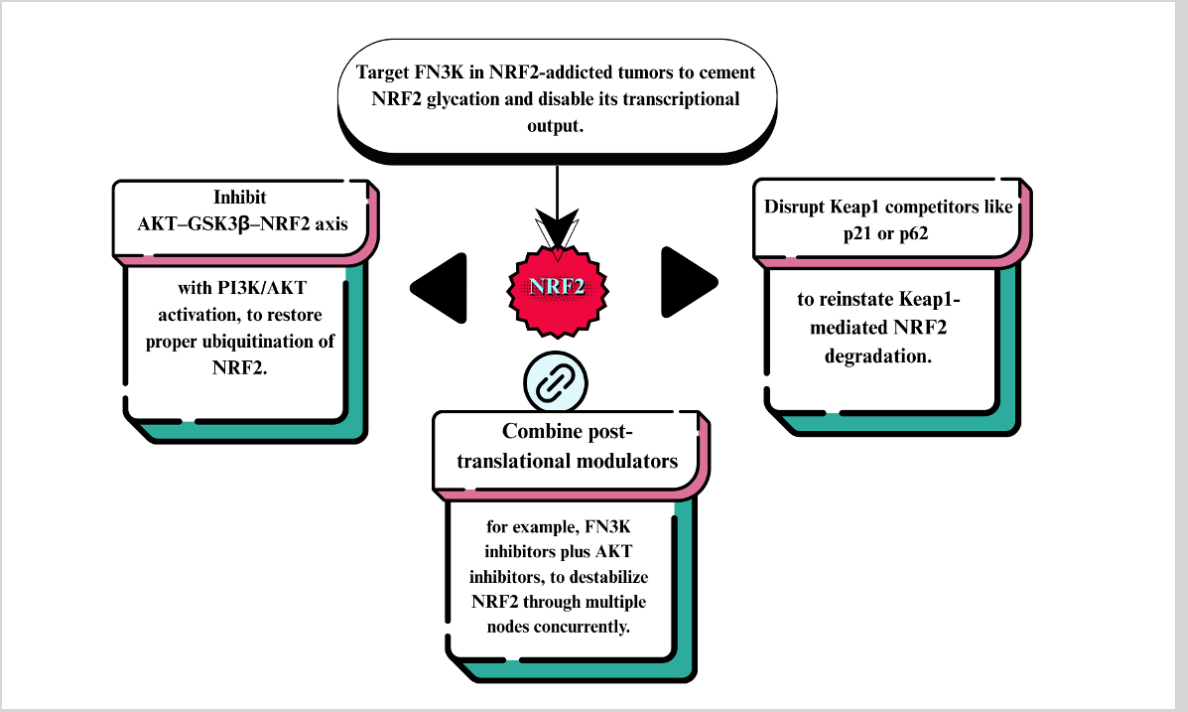

Figure 1. Multinodal strategy for destabilizing Nrf2 in cancer cells. This schematic illustrates four targeted approaches to suppress Nrf2 activity: (1) inhibiting FN3K to maintain NRF2 glycation and impair antioxidant gene transcription; (2) blocking the AKT–GSK3β axis to restore β-TrCP–mediated NRF2 degradation; (3) disrupting NRF2-stabilizing competitors like p21 and p62 to reinstate Keap1-dependent ubiquitination; and (4) combining FN3K and AKT inhibitors to concurrently destabilize Nrf2 through deglycation and phosphorylation-dependent degradation pathways. (we used Bio-render software for this illustration).

These approaches provide a multidimensional mechanistic strategy, each entry point (glycation, phosphorylation, Keap1 competition) is grounded in specific structural or amino-acid-level changes, with demonstrable effects on Nrf2 activity and tumor phenotypes in vivo, offering potent avenues for next-generation oncology therapies.

This suggests that selective modulation of the GSK-3β/Nrf2 axis can influence mitochondrial turnover and cellular redox homeostasis, processes that are often dysregulated in cancer cells. To sum up, these studies elucidate the multifaceted role of Nrf2 in integrating signaling pathways that govern cell survival, metabolism, and stress responses in digestive system cancers. The modulation of Nrf2 through the PI3K/AKT/GSK-3β axis, its interaction with p62, and its influence on growth factor signaling underscore its potential as a therapeutic target in oncology (Table 2).

Table 2. Post-translational mechanisms regulating NRF2 activity

Modification	Enzyme/Mechanism	Functional Outcome
Glycation	Reversible by FN3K	Disrupts DNA binding, reduces antioxidant transcription
Ubiquitination	Keap1–Cul3, β-TrCP	Degradation via proteasome
Phosphorylation	GSK3β (inhibited by AKT)	Promotes β-TrCP–mediated degradation
Keap1 competition	p21, p62, PGAM5	Stabilizes Nrf2

Keap1, Kelch-like ECH-associated protein 1; Cul3, cullin 3; β-TrCP, beta-transducin repeat-containing protein; GSK3β, glycogen synthase kinase 3 beta; AKT, protein kinase B; PGAM5, phosphoglycerate mutase family member 5.

3. Nrf2 as a Metabolic Integrator: Crosstalk with HIF-1α, AMPK, and Oncometabolite Networks in Tumor Progression

In addition, Nrf2 promotes tumor progression by inducing angiogenesis through the stimulation of HIF-1α-dependent expression of vascular endothelial growth factor (VEGF) in cancer cells(29, 61). HIF-1α is rapidly activated in response to acute hypoxic stress, triggering the upregulation of genes involved in glycolytic reprogramming and cell cycle arrest(29). Conversely, under prolonged hypoxia, HIF-2α activation occurs more gradually, enhancing the expression of genes associated with erythropoiesis and the maintenance of tumor stemness. In contrast to hypoxia, the condition of hyperoxia—defined by elevated partial pressures of oxygen—elicits profound cellular stress through the excessive generation of ROS, which impairs the structural integrity of nucleic acids, lipids, and proteins(60). This oxidative burden, if unresolved, can culminate in irreversible macromolecular damage and cell death. As a compensatory mechanism, cells engage a highly conserved redox-responsive transcriptional network to mitigate ROS toxicity and initiate repair of damaged components(46, 60). At the core of this adaptive response lies the transcription factor NRF2, which is rapidly stabilized and translocated to the nucleus under oxidative stress conditions.

Once activated, NRF2 binds to AREs in the promoters of a wide array of cytoprotective genes, including those involved in glutathione biosynthesis, NADPH regeneration, and xenobiotic metabolism(45, 46). This transcriptional reprogramming facilitates the detoxification of ROS, restoration of redox homeostasis, and repair of oxidative lesions, thereby promoting cellular survival in hyperoxic environments. The NRF2 axis thus represents a critical molecular determinant of cellular resilience against hyperoxia-induced cytotoxicity, underscoring its broader role in maintaining tissue integrity during oxidative insult. However, HIF-1α plays a pivotal role in metabolic reprogramming under hypoxic conditions by orchestrating several adaptive responses that favor cancer cell survival and proliferation. It inhibits mitochondrial oxidative phosphorylation through the transcriptional activation of lactate dehydrogenase A (LDHA) and pyruvate dehydrogenase kinase 1 (PDK1), thereby promoting a glycolytic phenotype. Concurrently, HIF-1α enhances glucose uptake by upregulating glucose transporter 4 (GLUT4), facilitating efficient ATP production with minimal ROS generation in oxygen-deprived environments. On the other hand, it is important to mention that ROS have been shown to promote the stabilization of HIF-1α by attenuating the enzymatic activity of prolyl hydroxylase domain-containing proteins (PHDs), thereby preventing the oxygen-dependent

degradation of HIF-1α under hypoxic conditions(63). Intriguingly, during prolonged hypoxic exposure, a compensatory mitochondrial adaptation is observed, wherein the production of mitochondrial ROS is diminished. This attenuation is mechanistically linked to the isoform-specific substitution of subunits within the cytochrome c oxidase complex, culminating in enhanced electron transfer efficiency and reduced electron leakage—a process that serves to modulate the cellular redox state and fine-tune the hypoxic response(64). This metabolic shift not only sustains energy production but also supports cancer cell proliferation.

Moreover, HIF-1α contributes to cellular homeostasis under hypoxic stress by inducing autophagy through the upregulation of BNIP3, which mediates the clearance of damaged organelles, particularly dysfunctional mitochondria(65). Additionally, it attenuates global protein synthesis by modulating key translational regulators, thereby conserving energy and preventing proteotoxic stress associated with unfolded protein accumulation(66).

In parallel, we can say that there is a metabolic collaboration between HIF-1α and Nrf2, wherein Nrf2 acts as a central regulator of redox balance, metabolic adaptation, and oncogenic survival(45). Through the transcriptional activation of genes involved in antioxidant defense and detoxification, such as those governing glutathione (GSH) biosynthesis and its recycling, Nrf2 shields cancer cells from oxidative damage and chemotherapeutic insults(43, 45). Furthermore, Nrf2 orchestrates a broad metabolic reprogramming that extends beyond redox regulation, notably stimulating the pentose phosphate pathway (PPP) through the transcriptional upregulation of glucose-6-phosphate dehydrogenase (G6PD) and 6-phosphogluconate dehydrogenase, thereby promoting nucleotide biosynthesis and NADPH generation essential for anabolic growth and antioxidant defense(23, 43). In parallel, Nrf2 modulates glutaminolysis by enhancing the expression of glutaminase and related enzymes, facilitating the replenishment of tricarboxylic acid (TCA) cycle intermediates and supporting biosynthetic flux(23, 24). Additionally, Nrf2 activation has been implicated in the regulation of lipid metabolism through increased expression of enzymes such as ATP-citrate lyase (ACLY) and fatty acid synthase (FASN), linking redox balance with membrane synthesis and energy storageCollectively, these Nrf2-driven metabolic rewiring events, spanning glycolysis, glutaminolysis, and redox buffering, support anabolic growth and stress adaptation in cancer cells. Their coordinated activation highlights Nrf2's central role in sustaining tumor bioenergetics and redox equilibrium under therapeutic pressure (67, 68) (Table 3).

Table 3. NRF2-mediated regulation of cancer cell metabolic pathways

Pathway	NRF2 Role	Transcriptional Targets
Glycolysis	Upregulates glycolytic enzymes in coordination with HIF-1α	HK2, PFKFB3, PKM2, LDHA
PPP	Increases NADPH + nucleotide synthesis	G6PD, 6PGD
Glutaminolysis	Supports TCA anaplerosis & biosynthesis	GLS1, ME1
Lipogenesis	Supports membrane synthesis & energy storage	ACLY, FASN
Redox buffering	Drives glutathione & thioredoxin systems	GCLC, GCLM, NQO1, TXNRD1

HIF-1α; hypoxia-inducible factor 1-alpha, HK2; hexokinase 2, PFKFB3; 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3, PKM2; pyruvate kinase M2, LDHA; lactate dehydrogenase A, NADPH; nicotinamide adenine dinucleotide phosphate, G6PD; glucose-6-phosphate dehydrogenase, 6PGD; 6-phosphogluconate dehydrogenase, TCA; tricarboxylic acid cycle, GLS1; glutaminase 1, ME; malic enzyme 1, ACLY; ATP citrate lyase, FASN; fatty acid synthase, GCLC; glutamate-cysteine ligase catalytic subunit, GCLM; glutamate-cysteine ligase modifier subunit, NQO1; NAD(P)H quinone dehydrogenase 1, TXNRD1; thioredoxin reductase 1.

Beyond metabolic reprogramming, Nrf2 regulates the expression of growth-related genes, including insulin-like growth factor 1 (IGF-1) and bone morphogenetic protein receptor 1 (BMPR1), as demonstrated by ChIP-seq analyses. These regulatory functions position Nrf2 as a critical mediator of cancer cell proliferation and survival (69).

Immunohistochemical analysis has revealed a progressive upregulation of Nrf2 and IGF-1 expression across the spectrum of gastric lesions, from benign to malignant transformation. In normal gastric tissue, both markers were absent, while benign hyperplastic polyps showed minimal or no expression, suggesting limited involvement in early tissue changesHowever, in premalignant lesions such as low-grade intraepithelial neoplasia, Nrf2 expression significantly increased, with 13 cases showing high and 25 intermediate levels, supported by a statistically significant trend. IGF-1 expression also rose markedly in these stages, with a considerable number of cases exhibiting high or intermediate levels. These findings suggest that Nrf2 supports tumor progression via redox regulation, while IGF-1 enhances cell proliferation and survival, together fostering a microenvironment conducive to carcinogenesis (70).

Oncometabolites, aberrant metabolic byproducts arising from mutations in metabolic enzymes such as isocitrate dehydrogenase (IDH), succinate dehydrogenase (SDH), and fumarate hydratase (FH), play a pivotal role in modulating transcriptional regulators like HIF-1α and Nrf2 in digestive system cancers(71). These oncometabolites, including 2-hydroxyglutarate (2-HG), succinate, and fumarate, accumulate due to disruptions in the tricarboxylic acid (TCA) cycle, leading to profound effects on cellular signaling pathways(72, 73).

Under normoxic conditions, HIF-1α is hydroxylated by PHD enzymes, marking it for proteasomal degradation(71, 74). However, elevated levels of oncometabolites like succinate and fumarate inhibit PHD activity by mimicking α-ketoglutarate, a co-substrate for PHDs, thereby preventing HIF-1α hydroxylation and subsequent degradation. This inhibition results in the stabilization and accumulation of HIF-1α, even in the presence of normal oxygen levels, promoting a pseudohypoxic state that facilitates angiogenesis, metabolic reprogramming, and tumor progression(74-76).

Similarly, oncometabolites influence the Nrf2 pathway(57, 76). Under basal conditions, Nrf2 is sequestered in the cytoplasm by Keap1, leading to its ubiquitination and degradation. However, increased ROS levels, often a consequence of oncometabolite accumulation, modify cysteine residues on Keap1, impairing its ability to target Nrf2 for degradation. This modification allows Nrf2 to translocate into the nucleus, where it activates the transcription of ARE-driven genes, enhancing the cellular antioxidant capacity and promoting survival under oxidative stress. Notably, oncometabolites such as fumarate and succinate, accumulated due to loss-of-function mutations in fumarate hydratase (FH) and succinate dehydrogenase (SDH), respectively, can lead to the post-translational modification of cysteine residues on Keap1 through processes like succination (as in the case of fumarate forming S-(2-succinyl) cysteine adducts) These modifications impair Keap1's ability to target Nrf2 for ubiquitination and degradation, thereby stabilizing Nrf2 and facilitating its nuclear translocation and transcriptional activation of cytoprotective genes (57, 76, 77).

The concurrent stabilization of HIF-1α and activation of Nrf2 by oncometabolites establishes a synergistic environment that supports tumor growth and resistance to therapy. HIF-1α drives the expression of genes involved in glycolysis and angiogenesis, adapting the tumor to hypoxic conditions, while Nrf2 enhances the antioxidant defenses, protecting cancer cells from oxidative damage. Recent evidence underscores a robust mechanistic link between Nrf2 and HIF-1α in promoting metabolic reprogramming in breast cancer, particularly through the regulation of glycolytic enzymes(29). Mechanistically, Nrf2 appears to exert this regulatory effect through modulation of AMPK and AKT signaling, whereby its knockdown activates AMPK and inhibits AKT, shifting the cellular metabolism away from glycolysis(29). In contrast, when NRF2 is knocked down, the balance tips toward AMPK activation and AKT inhibition, switching metabolism toward oxidative phosphorylation—a less efficient pathway for rapid growth (29, 78-80)

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On the other hand, in U251 glioma cells, which exhibited the highest endogenous expression of Nrf2 among tested glioma lines, Nrf2 was identified as a central regulator of redox homeostasis and cellular proliferation(81). Functionally, Nrf2 silencing led to a time-dependent inhibition of cell proliferation, with a 37.1% reduction by day 3 and 45.2% by day 4 ,alongside diminished colony size and number in clonogenic assays(81). Mechanistic assays revealed a significant drop in intracellular ATP levels, triggering an elevated AMP/ATP ratio and activation of AMPK, evidenced by increased AMPK phosphorylation(80, 81). This activation suppressed mTOR signaling, as reflected in decreased phosphorylation of both mTOR and p70S6K. In simple terms, when the cell senses low energy, AMPK "flips" a switch that turns off pathways (like mTOR) that normally drive growth and division. Pharmacological activation of AMPK using phenformin recapitulated these effects, further validating the Nrf2–AMPK–mTOR axisThis interplay between Nrf2, AMPK, mTOR, and p70S6K highlights their coordinated regulation of energy metabolism and proliferative signaling. A substantial body of evidence highlights the tightly coordinated interplay between NRF2 and key metabolic regulators such as AMPK, mTOR, p62, and KHK. This integrated signaling network governs cancer cell fate by fine-tuning bioenergetic balance, redox resilience, and proliferative signaling under stress conditions (79, 81). (Table 4). Collectively, these pathways converge to govern a multifaceted regulatory paradigm, the elucidation of which offers critical insights for therapeutic targeting and informed clinical decision-making aimed at improving prognosis and treatment outcomes.

Table 4. NRF2 integration within oncogenic signaling pathways and cellular outcomes

Pathway	NRF2 Interaction	Cellular Outcome
AMPK–mTOR	NRF2 silencing → AMPK↑ → mTOR↓	Proliferation ↓, energy preservation ↑
HIF-1α	NRF2 stabilizes HIF-1α; co-induce glycolysis	Hypoxia tolerance ↑, angiogenesis ↑
IGF-1/AKT	AKT inhibits GSK3β → NRF2 stabilization	Growth signal amplification
p53/p21	p21 binds NRF2 DLG/ETGE motifs	Blocks Keap1 binding → enhances NRF2 survival axis

AMPK, AMP-activated protein kinase; mTOR, mechanistic target of rapamycin; HIF-1α, hypoxia-inducible factor 1-alpha; IGF-1, insulin-like growth factor 1; AKT, protein kinase B; GSK3β, glycogen synthase kinase 3 beta; DLG, Asp-Leu-Gly motif; ETGE, Glu-Thr-Gly-Glu motif.

4-Conclusion

In summary, this review delineates NRF2 as a central regulatory nexus that integrates a constellation of intracellular stress cues, including oxidative perturbations, metabolic dysregulation, ER stress, nutrient deprivation, and hypoxic adaptation into a unified, context-sensitive survival framework. Functioning through dynamic cross-talk with Keap1, p62, SESN2, ATF4, AMPK, and HIF-1α, NRF2 governs a transcriptional landscape that sustains redox homeostasis, autophagic clearance, and metabolic flexibility under oncogenic and microenvironmental stress (Figure 2). This emerging layer of control reframes NRF2 not merely as a redox sentinel but as a decision-making node at the intersection of cell fate, stemness, and therapeutic resistance. While NRF2 activation promotes tumor cell survival and plasticity, its aberrant regulation may paradoxically expose targetable vulnerabilities, particularly in metabolically

reprogrammed or therapy-adapted malignancies. Thus, a nuanced understanding of this integrated signaling architecture opens avenues for precision oncology strategies that exploit the stress-adaptive liabilities encoded within the NRF2 network.

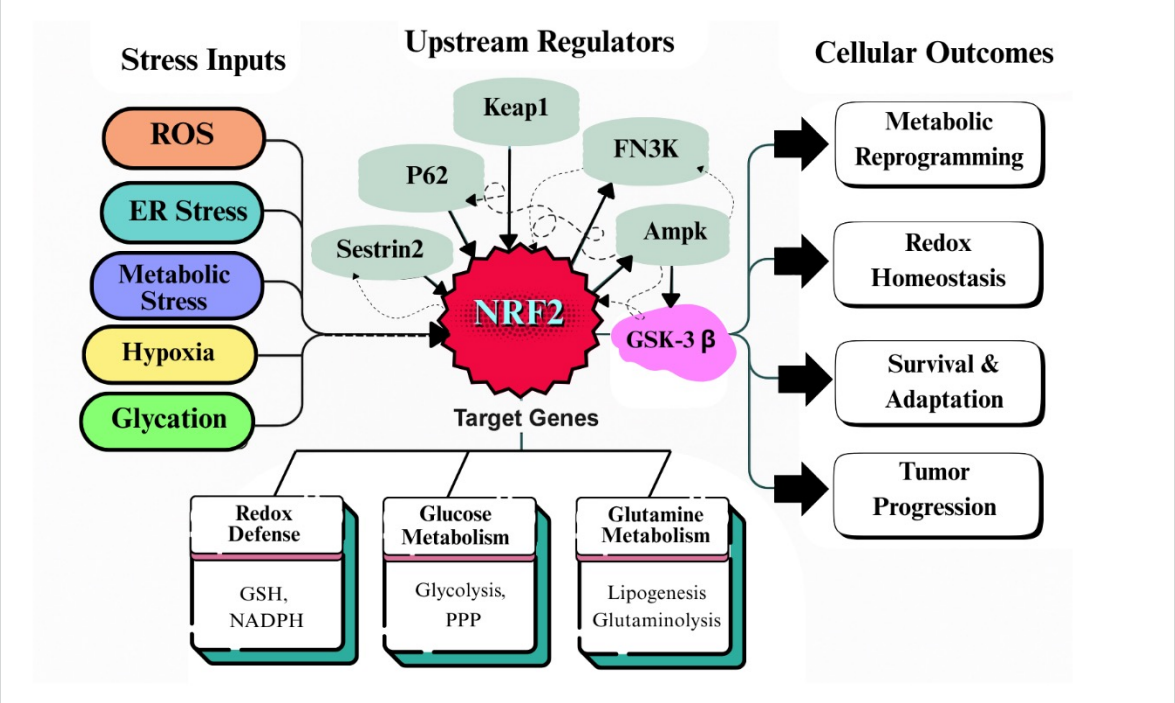

Figure 2. NRF2-centered regulatory architecture in oxidative and metabolic stress adaptation. The schematic illustrates how NRF2 integrates oxidative stress (via Keap1 oxidation, FN3K-mediated deglycation), metabolic stress (via AMPK–mTORC1), and ER/nutrient signals (GCN2–eIF2α–ATF4–SESN2), alongside hypoxic pathways involving HIF-1α. Scaffold proteins (e.g., p62, SESN2, AXIN) localize signal integration to subcellular compartments. FN3K-mediated deglycation of NRF2 acts as a post-translational switch modulating its transcriptional activation. Dashed arrows represent feedback and feedforward interactions based on stress intensity and context. (we used Bio-render software for this illustration).

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Alphabetical List of Abbreviations:

2-HG – 2-Hydroxyglutarate
6PGD – 6-Phosphogluconate Dehydrogenase
ACLY – ATP-Citrate Lyase
AGEs – Advanced Glycation End Products
AKT – Protein Kinase B
AMPK – AMP-Activated Protein Kinase
ARE – Antioxidant Response Element
BACH1 – BTB and CNC Homology 1
BACH2 – BTB and CNC Homology 2
bZIP – Basic Leucine Zipper
β-TrCP – Beta-Transducin Repeat-Containing Protein
BNIP3 – BCL2 Interacting Protein 3
CBP – CREB-Binding Protein
ChIP – Chromatin Immunoprecipitation
EGFR – Epidermal Growth Factor Receptor
EpREs – Electrophile Response Elements (AREs)
FASN – Fatty Acid Synthase
FH – Fumarate Hydratase
FN3K – Fructosamine-3-Kinase
G6PD – Glucose-6-Phosphate Dehydrogenase
GCLC – Glutamate-Cysteine Ligase Catalytic Subunit
GCL – Glutamate-Cysteine Ligase
GCLM – Glutamate-Cysteine Ligase Modifier Subunit
GLS1 – Glutaminase 1
GLUT4 – Glucose Transporter 4
GPX2 – Glutathione Peroxidase 2
GSH – Glutathione
HIF-1α – Hypoxia-Inducible Factor 1-alpha
HK2 – Hexokinase 2
HO-1 – Heme Oxygenase 1
HMOX1 – Heme Oxygenase 1
IDH – Isocitrate Dehydrogenase
IGF-1 – Insulin-Like Growth Factor 1
Keap1 – Kelch-Like ECH-Associated Protein 1
KHK – Ketohexokinase (Fructokinase)
KRAS – Kirsten Rat Sarcoma Viral Oncogene Homolog
LC-MS/MS–Liquid Chromatography-Tandem Mass Spectrometry
LDHA – Lactate Dehydrogenase A
MAREs – MAF Recognition Elements
ME1 – Malic Enzyme 1
mTOR – Mechanistic Target of Rapamycin
NAC – N-Acetyl Cysteine
NADPH – Nicotinamide Adenine Dinucleotide Phosphate (Reduced)
Neh domains – Nrf2-ECH Homology Domains
NQO1 – NAD(P)H Quinone Dehydrogenase 1
NRF2 – Nuclear Factor Erythroid 2–Related Factor 2
PDAC – Pancreatic Ductal Adenocarcinoma
PDGFR – Platelet-Derived Growth Factor Receptor
PDK1 – Pyruvate Dehydrogenase Kinase 1
PFKFB3–6-Phosphofructo-2-Kinase/Fructose-2,6-Bisphosphatase 3
PGAM5 – Phosphoglycerate Mutase Family Member 5
p21 – Cyclin-Dependent Kinase Inhibitor 1A (CDKN1A)
p53 – Tumor Protein p53
p62 / SQSTM1 – Sequestosome 1
p-p70 S6 kinase – Phosphorylated p70 Ribosomal S6 Kinase
PHDs – Prolyl Hydroxylase Domain-Containing Proteins
PI3K – Phosphoinositide 3-Kinase
PKM2 – Pyruvate Kinase M2
PPP – Pentose Phosphate Pathway
ROS – Reactive Oxygen Species
sMAF – Small Musculoaponeurotic Fibrosarcoma (Small Maf)
SDH – Succinate Dehydrogenase
SESN2 – Sestrin 2
TCA – Tricarboxylic Acid
Txnrd1 – Thioredoxin Reductase 1
VEGF – Vascular Endothelial Growth Factor