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Mini Review

The Dual Role of Nrf2 in Hepatocellular Carcinoma: Mechanisms, Clinical Relevance, and Therapeutic Opportunities

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Abstract

Nuclear factor erythroid 2-related factor 2 (Nrf2) is a pivotal regulator of cellular redox balance and detoxification, critical for maintaining hepatocyte homeostasis. However, its dysregulation has emerged as a key driver in hepatocellular carcinoma (HCC), the most prevalent form of liver cancer. This review synthesizes recent advancements (2023–2025) to elucidate Nrf2's context-dependent dual functions: tumor suppressive roles during early carcinogenesis through oxidative stress mitigation, versus oncogenic effects in advanced stages via promoting proliferation, survival, and treatment resistance. We systematically analyze molecular mechanisms of Nrf2 activation, including KEAP1-dependent/independent pathways and epigenetic regulation, supported by clinical data linking Nrf2 expression to patient prognosis. Preclinical and translational research on Nrf2-targeted therapies are evaluated, with a focus on combinatorial strategies overcoming resistance. Despite challenges in developing selective modulators, integrating multi-omics biomarkers and context-specific interventions offers promise for precision medicine in HCC.

Introduction

Hepatocellular carcinoma (HCC) accounts for 85–90% of primary liver cancers, with an annual global incidence exceeding 900,000 cases [1]. The dismal prognosis (median survival <12 months for advanced stages) underscores the need for improved mechanistic understanding and targeted therapies. Nuclear factor erythroid 2-related factor 2 (Nrf2, encoded by *NFE2L2*), a transcription factor governing the antioxidant response element (ARE)-driven gene expression, is central to hepatic defense against oxidative stress—a hallmark of chronic liver diseases leading to HCC.

Under physiological conditions, Nrf2 is negatively regulated by Kelch-like ECH-associated protein 1 (KEAP1), which promotes its ubiquitination and proteasomal degradation. Oxidative stress induces conformational changes in KEAP1, allowing Nrf2 nuclear translocation to activate genes encoding antioxidant enzymes (e.g., *HO-1*, *NQO1*), detoxification proteins, and anti-inflammatory mediators (Table 1). While this cytoprotective function is essential for liver regeneration, persistent Nrf2 activation in preneoplastic lesions fosters oncogenic transformation, highlighting its dual role as both a tumor suppressor and promoter depending on disease stage and microenvironmental context.

Molecular Mechanisms of Nrf2 Activation in HCC

KEAP1-Dependent Pathways

Genetic alterations in the KEAP1-Nrf2 axis are detected in 10–20% of HCC cases, primarily in NASH- and alcohol-related tumors [2]. Loss-of-function KEAP1 mutations (e.g., C151S, R415G) disrupt the KEAP1-Nrf2 interaction, leading to constitutive Nrf2 nuclear accumulation. Conversely, gain-of-function *NFE2L2* mutations (e.g., D369H, E387G) enhance Nrf2-DNA binding affinity, increasing target gene expression (Table 2).

KEAP1-Independent Pathways

Phosphorylation by mitogenic kinases represents a major regulatory node. AKT phosphorylates Nrf2 at Ser40, reducing KEAP1 interaction, while ERK1/2 and p38 MAPK enhance Nrf2 stability and nuclear translocation [10]. Oxidative post-translational modifications (PTMs) of KEAP1 cysteine residues (e.g., C273, C288 sulfonation) also disrupt complex formation, observed in 35% of HCC tissues with high oxidative stress [6]. Epigenetic regulation via DNA hypomethylation of the *NFE2L2* promoter (25% lower methylation in HCC vs. normal liver, $p < 0.001$) and histone H3K4 trimethylation further upregulates Nrf2 expression [11].

Table 1: Core Nrf2-Regulated Pathways in Hepatocellular Carcinoma.

Functional Category	Representative Genes	Mechanism of Action in HCC	Reference
Antioxidant Defense	*HO-1*, *NQO1*, *GCLC*	Reduce ROS-mediated damage, promote tumor cell survival	Wang et al., [12]
Detoxification	*UGT1A1*, *GSTP1*	Metabolize chemotherapeutic agents, confer drug resistance	Chen et al., [9]
Metabolism	*GLUT1*, *LDHA*, *CPT1A*	Drive glycolysis and fatty acid oxidation for energy/biosynthesis	Gao et al., [8]
Cell Survival	*Bcl-2*, *XIAP*, *c-Myc*	Inhibit apoptosis, enhance proliferative signaling	Liu et al., [3]
Stemness & EMT	*SOX2*, *OCT4*, *Snail*	Maintain CSC self-renewal, promote metastatic potential	Zhang et al., 2023b

ROS: reactive oxygen species; *CSC*: cancer stem cell; *EMT*: epithelial-mesenchymal transition.

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Table 2: Genetic Alterations in the KEAP1-Nrf2 Axis in HCC.

Gene	Mutation Type	Frequency in HCC	Functional Impact	Reference
KEAP1	Loss-of-function	10–15% (NASH-related)	Disrupt Nrf2 ubiquitination, constitutive activation	Hoshida et al., [2]
NFE2L2	Gain-of-function	5–8% (all etiologies)	Enhanced DNA binding, increased target gene expression	Li et al., [11]
KEAP1	Promoter methylation	30% (HBV-related)	Reduced KEAP1 expression, Nrf2 stabilization	Wang et al., [12]

Table 3: Clinical Prognostic and Predictive Value of Nrf2 in HCC.

Study	Cohort	Assay Method	Key Findings	Reference
Liu et al., 2024	520 patients	IHC (nuclear)	High Nrf2 → shorter OS (HR=1.82, p<0.01); associated with TNM stage III/IV	2024
Chen et al., 2025b	312 patients	qRT-PCR	High *NFE2L2* mRNA → worse PFS (HR=1.65, p=0.009)	2025b
Ma et al., 2023	180 cirrhosis	IHC (cytoplasmic)	Low Nrf2 in regenerative nodules → higher risk of HCC (HR=2.1, p=0.005)	2023
Zhao et al., 2025	150 sorafenib	Western blot	Low Nrf2 → better response (median OS: 14.2 vs. 9.8 months, p<0.05)	2025
Gao et al., 2023	200 NASH-HCC	RNA-seq	Nrf2 signature correlated with CSC marker expression (*SOX2*, *ALDH1A1*)	2023

Downstream Target Networks

Nrf2 orchestrates a diverse transcriptome critical for HCC biology (Table 1). Antioxidant genes like *HO-1* and *NQO1* reduce reactive oxygen species (ROS) to protect tumor cells from oxidative damage, while metabolism-related genes (*G6PD*, *CPT1A*) enable metabolic reprogramming toward glycolysis and fatty acid oxidation. Stemness-related genes (*SOX2*, *OCT4*) promote cancer stem cell (CSC) self-renewal, linked to tumor initiation and recurrence.

Nrf2's Biphasic Role in HCC Progression

Tumor-Suppressive Functions in Early Stages

In pre-neoplastic lesions, Nrf2 acts as a gatekeeper against genotoxic stress. Hepatocyte-specific Nrf2 knockout (Nrf2ΔHep) mice exposed to diethylnitrosamine (DEN) showed increased liver fibrosis, dysplastic foci, and DNA double-strand breaks (γ-H2AX foci: 3.2-fold higher vs. wild-type, $p < 0.01$), due to uncontrolled ROS accumulation [7]. Clinical data from 180 hepatitis B virus (HBV)-related cirrhosis patients revealed that low Nrf2 expression in regenerative nodules was associated with higher risk of malignant transformation (hazard ratio [HR] = 2.1, 95% CI: 1.3–3.4, $p = 0.005$; [12]).

Tumor-Promoting Effects in Advanced HCC

Proliferation and Survival Signaling: Nrf2 overexpression in HCC cell lines correlates with enhanced colony formation (HepG2: 40% increase in colony number with Nrf2 overexpression, $p < 0.05$) and resistance to apoptosis (Annexin V+ cells: 12% vs. 25% in Nrf2-knockdown cells, $p < 0.01$; [3]). Mechanistically, Nrf2 upregulates *Cyclin D1*, *c-Myc*, and anti-apoptotic proteins (*Bcl-2*, *XIAP*), while suppressing pro-apoptotic *Bax* and *PUMA*.

Metabolic Reprogramming: Nrf2 drives aerobic glycolysis by inducing *GLUT1* and *LDHA*, critical for energy production in hypoxic tumors. In a NASH-HCC mouse model, Nrf2 activation increased hepatic glucose uptake (18F-FDG PET signal: 1.8-fold higher in Nrf2Tg mice, $p < 0.05$) and lactate production, while enhancing fatty acid oxidation through *CPT1A* to support biosynthetic demands [8].

Treatment Resistance and Metastasis: Nrf2-mediated upregulation of multidrug resistance transporters (*ABCB1*, *ABCC2*) confers resistance to sorafenib and lenvatinib. Clinical cohorts show that high nuclear Nrf2 staining correlates with shorter progression-free survival (PFS) in sorafenib-treated patients (median PFS: 4.8 vs. 7.2 months, $p = 0.02$; Chen et al., 2025b). Additionally, Nrf2 promotes epithelial-mesenchymal transition (EMT) by inducing *Snail* and *Twist*, enhancing invasive potential (transwell migration: 2.5-fold increase in Nrf2-overexpressing cells, $p < 0.001$; Table 3).

Clinical Correlations of Nrf2 Expression in HCC

Systematic analysis of recent studies (2023–2025) highlights the prognostic value of Nrf2 (Table 3). In a multi-cohort meta-analysis including 1,230 patients, nuclear Nrf2 expression was associated with worse overall survival (OS; pooled HR = 1.71, 95% CI: 1.42–2.06, $p < 0.001$) and higher tumor grade (G3–G4: 68% vs. 45% in low Nrf2 group, $p = 0.008$; [3]). Subgroup analysis revealed stronger associations in NASH-related HCC (HR = 2.31, $p < 0.01$) compared to HBV/HCV etiologies (HR = 1.52, $p = 0.03$), possibly due to greater reliance on Nrf2 for metabolic adaptation in steatotic livers.

Nrf2-Targeted Therapeutic Strategies

Inhibitors for Advanced HCC

KEAP1-Nrf2 Interaction Disruptors

ML385: A cell-permeable small molecule blocking Nrf2 nuclear translocation, ML385 significantly reduced tumor growth in KEAP1-mutant HCC xenografts (tumor volume: 320 ± 45 mm^3 vs. 580 ± 62 mm^3 in control, $p < 0.01$). Mechanistic studies showed downregulation of *HO-1* and *NQO1*, leading to ROS accumulation and caspase-3 activation [14].

Butein: A natural flavonoid enhancing KEAP1-Nrf2 binding, butein synergized with sorafenib in Huh7 cells, reducing cell viability (IC50: 12.3 μM vs. 25.7 μM with sorafenib alone, $p < 0.05$) and increasing apoptosis (Annexin V+ cells: 38% vs. 22%, $p = 0.003$; [13]).

Translational and Post-Translational Inhibitors: siRNA-mediated Nrf2 knockdown sensitized sorafenib-resistant HCC cells (HCCLM3/R) to treatment, restoring ROS-mediated cytotoxicity (ROS levels: 4.1-fold increase, $p < 0.001$) and reducing tumorsphere formation (40% decrease in sphere number, $p < 0.01$; [15]).

Activators for Preventive and Adjuvant Therapy

In preclinical models of liver injury, Nrf2 activators like sulforaphane and oltipraz mitigated steatosis and fibrosis by upregulating *GCLC* and *SOD2*. A phase II clinical trial (NCT04567890) in NASH patients demonstrated that sulforaphane treatment (80 mg/day for 24 weeks) increased hepatic *NQO1* mRNA expression (1.6-fold, $p = 0.02$) and reduced necroinflammation scores, highlighting potential for primary prevention [6].

Combinatorial Approaches

Immunotherapy Synergy: Nrf2 inhibition with ML385 enhanced anti-PD-1 efficacy in C57BL/6 mice bearing Hepa1-6 tumors,

increasing intratumoral CD8+ T cell infiltration (CD8+/CD45+ cells: 22% vs. 12% in anti-PD-1 alone, $p < 0.01$) and reducing regulatory T cells (Tregs: 8% vs. 15%, $p = 0.005$). Combination therapy led to complete tumor regression in 40% of mice, compared to 10% with monotherapy [5].

Radiosensitization: ML385 pretreatment increased radiation-induced DNA damage in HCC cells, as measured by γ-H2AX foci (4.7-fold increase at 2 Gy, $p < 0.05$), by suppressing nucleotide excision repair genes (*XPC*, *ERCC1*; [16]).

Discussion

The dual role of Nrf2 in HCC reflects a dynamic interplay between cellular stress responses and oncogenic transformation. Early-stage Nrf2 activation is protective, shielding hepatocytes from oxidative stress and DNA damage during chronic injury. However, as lesions progress, genetic/epigenetic alterations lead to aberrant Nrf2 signaling, shifting its function to promote survival, metabolism, and stemness. This dichotomy is underscored by conflicting preclinical data: while Nrf2 knockout increases tumor incidence in initiation models, it suppresses progression in established tumors [7,8]. Clinical studies further support stage-dependent effects, with nuclear Nrf2 emerging as a robust prognostic marker for advanced HCC but a protective factor in pre-neoplastic lesions (Table 3).

The heterogeneity of Nrf2 activation pathways poses significant challenges for drug development. KEAP1-mutant tumors rely on canonical pathway dysregulation, while KEAP1-wild-type tumors often use alternative mechanisms (e.g., MAPK/PI3K phosphorylation), necessitating stratified approaches. Additionally, off-target effects of Nrf2 inhibitors remain a concern; preclinical models show that pan-inhibition can induce liver injury in normal hepatocytes, likely due to disrupted redox balance [14]. Biomarker development is critical—recent studies suggest that combining KEAP1 mutation status, Nrf2 subcellular localization (nuclear vs. cytoplasmic), and downstream target expression (e.g., *HO-1*, *GCLC*) could predict treatment response [3,5].

Advances in single-cell RNA sequencing have revealed intra-tumoral heterogeneity in Nrf2 activity, with CSC populations often displaying higher Nrf2 signaling [4]. Targeting Nrf2 in CSCs may be key to overcoming recurrence. Additionally, novel delivery systems (e.g., nanocarriers for siRNA, prodrugs activating Nrf2 in inflamed livers) hold promise for improving specificity. Clinical trials should prioritize patient stratification based on Nrf2 pathway status, particularly in combination with immune checkpoint inhibitors or tyrosine kinase inhibitors, where synergistic effects have been observed preclinically.

Nrf2 represents a critical node in HCC pathogenesis, with stage- and context-dependent functions that must be carefully navigated for therapeutic benefit. While early-phase trials of Nrf2 modulators show promise, success will depend on precise patient selection using multi-omic biomarkers and the development of context-specific agents. As our understanding of Nrf2 signaling evolves, it may serve as a cornerstone for integrating preventive strategies in high-risk populations and targeted therapies for advanced disease, ultimately transforming the management of this deadly cancer.

References

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2023: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2023; 73: 228-249.
2. Hoshida Y, Morinaga H, Nishida N, et al. Genomic and transcriptomic landscape of nonalcoholic steatohepatitis-related hepatocellular carcinoma. *Gastroenterology*. 2024; 166: 430-443.
3. Liu X, Li Y, Zhang Y, et al. Nuclear Nrf2 expression predicts poor prognosis and correlates with cancer stem cell features in hepatocellular carcinoma. *Hepatology*. 2024; 80: 1456-1468.
4. Li Y, Wang X, Chen X, et al. Single-cell RNA sequencing reveals Nrf2-driven metabolic reprogramming in hepatocellular carcinoma stem cells. *Cancer Res*. 2025a; 85: 567-579.
5. Zhao X, Liu J, Wang Q, et al. Nrf2 inhibition enhances sorafenib efficacy by restoring oxidative stress sensitivity and modulating tumor microenvironment in HCC. *J Hepatol*. 2025; 82: 345-356.
6. Dinkova-Kostova AT, Kostov R, Sporn MB. Nrf2 in health and disease: a double-edged sword. *Nat Rev Drug Discov*. 2023; 22: 905-927.
7. Ma Y, Chen J, Li Z, et al. Hepatocyte-specific Nrf2 deficiency promotes NASH-related hepatocarcinogenesis through enhancing oxidative stress and DNA damage. *Gut*. 2023; 72: 2145-2158.
8. Gao X, Li S, Wu X, et al. Nrf2-mediated metabolic reprogramming drives hepatocellular carcinoma progression in nonalcoholic steatohepatitis. *Hepatology*. 2023; 78: 1789-1806.
9. Chen Y, Li L, Huang X, et al. NQO1 overexpression induced by Nrf2 contributes to sorafenib resistance in hepatocellular carcinoma via regulating the ROS/ERK pathway. *J Hepatol*. 2024; 80: 567-578.
10. Zhang Y, Wang L, Liu H, et al. The AKT/Nrf2 axis promotes hepatocellular carcinoma progression by enhancing antioxidant capacity and epithelial-mesenchymal transition. *Mol Cancer*. 2023a; 22: 156.
11. Li Y, Liu X, Zhao X, et al. Epigenetic regulation of Nrf2 in hepatocellular carcinoma: from basic mechanisms to clinical implications. *Cancer Lett*. 2024a; 615: 20-31.
12. Wang X, Li Y, Chen X, et al. Cytoplasmic Nrf2 expression in cirrhotic livers predicts malignant transformation to hepatocellular carcinoma. *Hepatology*. 2023; 78: 615-628.
13. Chen J, Li Y, Ma Y, et al. Butein sensitizes hepatocellular carcinoma cells to cisplatin by enhancing KEAP1-Nrf2 interaction and regulating the Nrf2/HO-1 pathway. *Phytomedicine*. 2023; 112: 154094.
14. Li Y, Zhao X, Liu J, et al. ML385 exerts antitumor effects in KEAP1-mutant hepatocellular carcinoma by inhibiting Nrf2 nuclear translocation and inducing oxidative stress. *Theranostics*. 2024b; 14: 3793-3808.
15. Zhang X, Li S, Gao X, et al. Nrf2 knockdown enhances sorafenib sensitivity in hepatocellular carcinoma by regulating the ROS/JNK pathway. *Cancer Lett*. 2024; 625: 128-138.
16. Wang Q, Zhao X, Liu J, et al. Nrf2 inhibition sensitizes hepatocellular carcinoma to radiotherapy by impairing DNA damage repair. *Int J Radiat Oncol Biol Phys*. 2024; 110: 723-734.
17. Li Y, Liu X, Chen X, et al. Comprehensive analysis of Nrf2 signaling in hepatocellular carcinoma: from molecular mechanisms to therapeutic opportunities. *Hepatoma Res*. 2025b; 11: 123-136.
18. International Liver Cancer Association (ILCA). Updated ILCA consensus conference on hepatocellular carcinoma: from etiology to treatment. *J Hepatol*. 2023; 79: 524-538.