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The dual role of nuclear factor erythroid 2-related factor 2 in hepatocellular carcinoma: mechanisms, clinical relevance, and therapeutic opportunities

Houhong Wang, Shang Bian*

Department of General Surgery, The Affiliated Bozhou Hospital of Anhui Medical University, Bozhou 236800, Anhui, China

***Correspondence:** Shang Bian, Department of General Surgery, The Affiliated Bozhou Hospital of Anhui Medical University, Bozhou 236800, Anhui, China. shangbian2018@163.com

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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 Kelch-like ECH-associated protein 1 (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 is 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.

Keywords

Hepatocellular carcinoma, nuclear factor erythroid 2-related factor 2, molecular mechanisms, targeted therapy

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.

Table 1. Core Nrf2-regulated pathways in HCC

Functional category	Representative genes	Mechanism of action in HCC	Reference
Antioxidant defense	*HO-1*, *NQO1*, *GCLC*	Reduce ROS-mediated damage, promote tumor cell survival	[10]
Detoxification	*UGT1A1*, *GSTP1*	Metabolize chemotherapeutic agents, confer drug resistance	[16]
Metabolism	*GLUT1*, *LDHA*, *CPT1A*	Drive glycolysis and fatty acid oxidation for energy/biosynthesis	[11]
Cell survival	*Bcl-2*, *XIAP*, *c-Myc*	Inhibit apoptosis, enhance proliferative signaling	[14]
Stemness & EMT	*SOX2*, *OCT4*, *Snail*	Maintain CSC self-renewal, promote metastatic potential	[20]

CSC: cancer stem cell; EMT: epithelial-mesenchymal transition; HCC: hepatocellular carcinoma; Nrf2: nuclear factor erythroid 2-related factor 2; ROS: reactive oxygen species

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 non-alcoholic steatohepatitis (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 protein has several structural domains, and its binding to Nrf2 is mainly dependent on the Kelch domain. Under normal conditions, KEAP1 binds to the DLG and ETGE motifs in the Neh2 domain of Nrf2 through specific amino acid residues in the Kelch domain to form a stable protein complex, which maintains Nrf2 in the cytoplasm and is ubiquitinated to keep it in a low activity state.

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	[2]
NFE2L2	Gain-of-function	5–8% (all etiologies)	Enhanced DNA binding, increased target gene expression	[6]
KEAP1	Promoter methylation	30% (HBV-related)	Reduced KEAP1 expression, Nrf2 stabilization	[10]

HBV: hepatitis B virus; HCC: hepatocellular carcinoma; KEAP1: Kelch-like ECH-associated protein 1; NASH: non-alcoholic steatohepatitis; Nrf2: nuclear factor erythroid 2-related factor 2

When a loss-of-function mutation such as C151S occurs, the cysteine at the C151 site is essential for maintaining the structural stability and redox sensitivity of KEAP1. Mutation to serine alters the local conformation of the KEAP1 structure and disrupts the precise matching of the Nrf2 binding interface. At the same time, the hydrogen bonding network and electrostatic interactions within the KEAP1 protein are also disturbed by the mutation, which prevents KEAP1 from binding to Nrf2 in the correct spatial conformation, and Nrf2 is freed from KEAP1, leading to constitutive nuclear accumulation and activation of downstream target genes.

For the R415G mutation, the arginine (R) residue is normally involved in key electrostatic interactions upon binding to Nrf2. Mutation of arginine to glycine (G) results in the loss of the originally positively charged side chain, greatly weakening the electrostatic attraction between KEAP1 and Nrf2, leading to a dramatic decrease in their binding affinity. This change in physical binding strength makes it difficult for KEAP1 to effectively anchor Nrf2, and ultimately disrupts the KEAP1-Nrf2 interaction, contributing to the sustained activation of Nrf2, which drives the expression of tumor-associated genes and affects the development of HCC [3].

KEAP1-independent pathways

Phosphorylation by mitogenic kinases represents a major regulatory node. Serine/threonine kinase (AKT) phosphorylates Nrf2 at Ser40, reducing KEAP1 interaction, while ERK1/2 and p38 MAPK enhance Nrf2 stability and nuclear translocation [4]. 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 [5]. 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 [6].

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. The activation of the glycolytic pathway enables tumor cells to preferentially generate energy through anaerobic metabolism even under aerobic conditions, and this metabolism not only rapidly provides ATP for tumor cell proliferation, but also generates a large number of intermediary metabolites for biomolecule synthesis to meet the needs of rapid growth of tumor cells; fatty acid oxidation provides a stable source of energy for tumor cells to adapt to the nutritional fluctuations in the tumor microenvironment [7]. Stemness-related genes (*SOX2*, *OCT4*) promote cancer stem cell (CSC) self-renewal, linked to tumor initiation and recurrence. CSCs with stem cell properties are capable of self-renewal, continuously generating new tumor cells to drive tumor initiation, growth, and metastasis. At the same time, CSCs are more resistant to chemotherapeutic agents and radiotherapy, and their highly expressed drug resistance-associated proteins can efflux drugs. Their low proliferative state makes them difficult to clear by conventional therapies targeting fast-proliferating cells, which can lead to tumor recurrence and poor patient prognosis, accelerating the progression of HCC [8].

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 [9]. Clinical data from 180 hepatitis B virus (HBV)-related cirrhosis patients revealed that low Nrf2 expression in regenerative nodules was associated with a higher risk of malignant transformation [hazard ratio (HR) = 2.1, 95% confidence interval (CI): 1.3–3.4, $p = 0.005$ [10]].

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, $p < 0.01$ [4]). 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 [11]. Nrf2-induced metabolic shifts have significant advantages for tumor cells. Enhanced glycolysis enables tumor cells to rapidly generate ATP, which can meet their energy requirements and sustain their survival and proliferation even under hypoxic conditions. Meanwhile, the intermediate metabolites generated by the glycolysis process, such as ribulose-5-phosphate and NADPH in the pentose phosphate pathway, provide raw materials for tumor cells to synthesize biomolecules such as nucleic acids, proteins, and lipids, and support their rapid growth. The enhancement of fatty acid oxidation not only provides tumor cells with a stable source of energy, but also generates substances such as acetyl coenzyme A, which participates in the tricarboxylic acid cycle and biosynthesis process, further satisfying the material and energy needs of tumor cells. In addition, lactic acid produced by glycolysis can acidify the tumor microenvironment, promote tumor cell invasion and metastasis, and inhibit the function of immune cells, helping tumor cells to evade immune surveillance for better survival and development.

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, $p = 0.02$ [12]). Nrf2 upregulates multidrug resistance transporters (ABCB1, ABCC2) by both direct and indirect mechanisms. In direct action, Nrf2 can directly bind to the ARE in the promoter region of ABCB1 and ABCC2 genes after entering the nucleus, and enhance the transcriptional activity of the genes by recruiting transcriptional coactivators, leading to the up-regulation of transporter expression, accelerating drug efflux, lowering the intracellular drug concentration, and triggering drug resistance. In the indirect mechanism, Nrf2 activation regulates the expression of downstream inflammatory factors (e.g., *IL-6*, *TNF-α*) or other transcription factors (e.g., *STAT3*), and these intermediary factors further combine with the regulatory regions of the ABCB1 and ABCC2 genes to synergistically enhance the transcription and expression of the transporter; at the same time, Nrf2 indirectly influences the multidrug-resistant transporter by regulating the redox state of the cell and altering the activity of the signaling pathway. At the same time, Nrf2 regulates the intracellular redox state and alters the activity of signaling pathways, indirectly affecting the expression level of multidrug resistance transporters, which together promote the development of HCC resistance to drugs such as sorafenib and lenvatinib [13]. 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). There is a strict and complicated link between Nrf2 and HCC metastasis. At the molecular level, Nrf2 directly drives the EMT process by inducing the expression of transcription factors such as *Snail* and *Twist*, causing cancer cells to lose polarity and intercellular junctions, and acquiring mesenchymal cellular characteristics, thus possessing stronger migration and invasive ability and creating conditions for distant metastasis. Meanwhile, Nrf2 activation can regulate extracellular matrix remodeling-related genes and promote the expression and secretion of matrix metalloproteinases (MMPs) and other proteins, which can degrade the basement membrane and extracellular matrix components, and help the cancer cells break through the tissue barrier, infiltrate into the surrounding tissues and enter into the circulatory system.

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, $p = 0.008$ [14]). Subgroup analysis revealed stronger associations in NASH-

Table 3. Clinical prognostic and predictive value of Nrf2 in HCC

Reference	Cohort	Assay method	Key findings
[14]	520 patients	IHC (nuclear)	High Nrf2 → shorter OS (HR = 1.82, $p < 0.01$); associated with TNM stage III/IV
[21]	312 patients	qRT-PCR	High *NFE2L2* mRNA → worse PFS (HR = 1.65, $p = 0.009$)
[9]	180 cirrhosis	IHC (cytoplasmic)	Low Nrf2 in regenerative nodules → higher risk of HCC (HR = 2.1, $p = 0.005$)
[19]	150 sorafenib	Western blot	Low Nrf2 → better response (median OS: 14.2 vs. 9.8 months, $p < 0.05$)
[11]	200 NASH-HCC	RNA-seq	Nrf2 signature correlated with CSC marker expression (*SOX2*, *ALDH1A1*)

CSC: cancer stem cell; HCC: hepatocellular carcinoma; HR: hazard ratio; IHC: immunohistochemistry; NASH: non-alcoholic steatohepatitis; Nrf2: nuclear factor erythroid 2-related factor 2; OS: overall survival; PFS: progression-free survival; qRT-PCR: quantitative reverse transcription-polymerase chain reaction; TNM: tumor node metastasis

related HCC (HR = 2.31, $p < 0.01$) compared to HBV/hepatitis C virus (HCV) etiologies (HR = 1.52, $p = 0.03$), possibly due to greater reliance on Nrf2 for metabolic adaptation in steatotic livers. This finding has important clinical significance. From the perspective of disease progression, the high activation of Nrf2 may indicate that NASH-associated HCC has entered a more aggressive stage, suggesting that clinicians should monitor Nrf2 expression more closely in HCC patients with NASH background as a complementary indicator for risk assessment of disease progression. Meanwhile, this subgroup analysis may help to develop diagnostic tools for Nrf2-related molecular features and improve the early detection rate of NASH-associated HCC. In terms of therapeutic strategy, for NASH-associated HCC, combination therapies with Nrf2 as the core can be considered. For example, Nrf2 inhibitors can be combined with existing anti-HCC drugs in targeted therapy to block the oncogenic pathway mediated by Nrf2 overactivation and enhance drug sensitivity. This will help to improve the success rate of clinical treatment.

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 [15].

Penfluridol

Penfluridol, a first-generation antipsychotic introduced in 1968, has shown favorable anticancer effects in both in vitro and in vivo studies, hindering the growth of a variety of cancer cell lines. Penfluridol treatment upregulates Nrf2 expression by modulating the interaction between KEAP1 and Nrf2. Tumor weight of mice treated with pentafluridine was significantly lower than that of mice treated with the vector (tumor volume 25 ± 13 mm^3 vs. 76 ± 25 mm^3 in control, $p < 0.01$ [16]).

Translational and post-translational inhibitors

Transcriptional and post-translational inhibitors act by targeting the transcriptional activation or PTM processes of Nrf2. Transcriptional inhibitors specifically bind to the Nrf2-DNA binding domain, preventing it from binding to the ARE and inhibiting the transcription of target genes, while PTM inhibitors focus on modifying the phosphorylation, acetylation and other processes of Nrf2, e.g., by inhibiting the activity of the relevant kinases or acetyltransferases, altering the stability and activity of Nrf2 to make it more susceptible to degradation by the proteasome. 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, $p < 0.01$ [17]).

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 [18].

Combinatorial approaches

Immunotherapy synergy

Nrf2 inhibition with ML385 enhanced anti-programmed cell death protein 1 (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 [19].

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*) [17].

Combination with other signaling pathway-targeting drugs

Phosphatidylinositol 4-phosphate 5-kinase 1α (PIP5K1A) competes for binding to the Kelch structural domain of KEAP1 in a kinase-independent manner, causing Nrf2 to escape ubiquitylation and degradation, and promotes Nrf2-dependent transcription and inhibits iron death. The PIP5K1A-specific inhibitor, ISA-2011B, can effectively inhibit HCC growth and enhance the sensitivity of HCC cells to sorafenib. ISA-2011B, a PIP5K1A-specific inhibitor, can effectively inhibit HCC growth and enhance the sensitivity of HCC cells to sorafenib, providing a theoretical basis for the combination of Nrf2-targeted therapy and PIP5K1A inhibition [13].

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 [9, 11]. 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 [15]. 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 [14, 19].

Advances in single-cell RNA sequencing have revealed intra-tumoral heterogeneity in Nrf2 activity, with CSC populations often displaying higher Nrf2 signaling [18]. 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.

Currently, studies on the mechanism of Nrf2 dual role in HCC are mostly based on cell models and animal experiments, and there are obstacles to clinical translation; clinical data are mostly focused on retrospective analysis, and there is a lack of prospective studies, which makes it difficult to accurately assess the impact of Nrf2 dynamics on the disease process. In addition, existing Nrf2-targeted therapies have not fully considered the patient etiology, tumor heterogeneity, and the complex interactions between upstream and downstream pathways of Nrf2 in clinical trials, leading to differences in therapeutic efficacy.

Conclusions

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. In the future, it is necessary to deeply investigate the dynamic regulatory mechanism of Nrf2 in HCC of different etiologies and stages, and analyze its cell-specific function in the tumor microenvironment by combining single-cell sequencing and other technologies; accelerate the development of multi-omics predictive biomarkers based on Nrf2 activity, and guide the precise stratification of therapies; and at the same time, strengthen the research and development of specific modulators targeting the key nodes of the Nrf2 pathway, and explore the new strategies of combination therapy, so as to promote the effective translation of Nrf2-targeted therapy into the clinical practice. At the same time, we will strengthen the research and development of specific modulators targeting key Nrf2 pathway nodes and explore new strategies for combination therapy, so as to promote the effective translation of Nrf2-targeted therapies into clinical practice. 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.

Abbreviations

ARE: antioxidant response element

CI: confidence interval

CSC: cancer stem cell

EMT: epithelial-mesenchymal transition

HBV: hepatitis B virus

HCC: hepatocellular carcinoma

HR: hazard ratio

KEAP1: Kelch-like ECH-associated protein 1

NASH: non-alcoholic steatohepatitis

Nrf2: nuclear factor erythroid 2-related factor 2

PD-1: programmed cell death protein 1

PFS: progression-free survival

PIP5K1A: phosphatidylinositol 4-phosphate 5-kinase 1α

PTMs: post-translational modifications

ROS: reactive oxygen species

Declarations

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The authors declare that they have no conflicts of interest.

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