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Review

# Balancing Act: NRF2's contradictory roles in cancer progression and therapy

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***ABSTRACT***

The nuclear factor erythroid 2-related factor 2 (NRF2) is an important cellular defense factor that regulates antioxidant and detoxifying gene expression. While NRF2 protects cells from oxidative stress, misregulation has been associated with cancer growth. Mutations in NRF2 or its inhibitor Kelch-like ECH-associated protein 1 can cause prolonged activation, which promotes tumor development, chemoresistance, and cancer cell survival. Understanding the NRF2 pathway is critical for designing targeted therapeutics, especially in cancers including lung, breast, and esophageal cancer, where NRF2 overexpression is associated with a poor prognosis and treatment resistance. The potential of NRF2 inhibitors in overcoming chemoresistance emphasizes their importance as a therapeutic target in cancer treatment. This review examines the molecular structure and regulatory mechanisms of NRF2, highlighting its dual role as both a tumor suppressor and an oncogene.

***Keywords:*** Cancer, chemoresistance, gene expression, NRF2, oxidative stress.

The nuclear factor erythroid 2-related factor 2 (NRF2), is one of the key genes involved in cellular defense mechanisms. This gene activates the transcriptional factor at the cellular level through its genetic codes when inflammation or injury occurs. The NRF2 is known for its function in regulating the expression levels of antioxidant proteins or peptides that play a role in protecting against oxidative damage at both the cellular and molecular levels. Under normal conditions, NRF2 exists in its inactive form in the cytoplasm, bound to Kelch-like ECH-associated protein 1 (KEAP1). Upon oxidative damage, inflammation, or injury, NRF2 is activated and dissociates from KEAP1, translocating to the nucleus. Through various vesicles, NRF2 passes through nuclear pores and binds to antioxidant response elements (AREs) located in the promoter regions of target genes, thereby regulating transcriptional activity.[1-3]

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Activated NRF2, having dissociated from KEAP1, leads to the upregulation of various cytoprotective genes, including those responsible for the synthesis of enzyme molecules such as NAD(P)H: quinone oxidoreductase 1 and glutathione S-transferases, which are involved in detoxification processes.[1,2] This mechanism holds significant importance in cancer biology, as NRF2 contributes to chemoresistance and, through its antioxidant properties, facilitates tumor growth, thereby promoting the survival of cancer cells. This response is critical for maintaining cellular redox balance and defending against the harmful effects of reactive oxygen species (ROS) produced by metabolic activities or environmental stressors. For example, studies have demonstrated that NRF2 activation can reduce the effects of xenobiotics and oxidative stress, preventing carcinogenesis and increasing cell survival.[4,5] For instance, mutations in KEAP1 or NRF2 itself result in the constitutive activation of NRF2, which has been observed in various types of cancer, including lung cancer.[6]

It is evident that NRF2 plays a role in numerous physiological functions, including spermatogenesis and male reproductive health. Genetic modifications leading to defects or

deficiencies in NRF2 can disrupt the chemistry of spermatogenesis. Polymorphisms have been identified in the NRF2 gene promoter, suggesting that genetic variations may influence individual susceptibility to oxidative stress-related diseases.[7]

## MOLECULAR STRUCTURE AND REGULATORY MECHANISMS OF NRF2 GENE

The molecular structure of NRF2 is characterized by several functional domains that facilitate its regulatory functions, including a basic leucine zipper (bZIP) domain required for dimerization and deoxyribonucleic acid binding and a Nrf2-ECH homology 2 (Neh2) domain that interacts with its repressor KEAP1.

The details of the molecular flow together with the interaction of the NRF2 gene with KEAP1 are available. The Neh2 domain facilitates ubiquitination and degradation of NRF2. It also facilitates its interaction with the KEAP1 molecule. The binding of KEAP1 to the NRF2 gene for its interaction has been indicated by molecular structural studies. The Neh2 domain carries specific motifs for KEAP1 recognition. It makes NRF2 a target for proteasomal degradation when oxidative stress levels are low.[8] The bZIP domain in NRF2 is a structural motif involved in molecular interactions. It enables NRF2 to interact with the sMaf protein, forming a functional heterodimer. This interaction is important for the binding of AREs located in the promoters of genes. This heterodimerization is important for the transcriptional activation of genes involved in antioxidant and detoxification processes.[9] Another molecular domain, Neh1, initiates the transcriptional processes of target genes. It accelerates the transcriptional process of NRF2 by molecular reaction with co-activators such as CBP/p-300.[10] The Neh3, another domain of NRF2 involved in transcriptional activation, is functional in the molecular regulation of NRF2.[11]

The KEAP1 molecule functions as an E3 ubiquitin ligase and retains NRF2 in the cytoplasm, assisting in its degradation. When cells are exposed to oxidative stress or electrophilic components, the KEAP-NRF2 interaction is disrupted, leading to stabilization and nuclear translocation of NRF2. The biochemical reactions occurring here stimulate the transcriptional process of many cytoprotective genes of NRF2. The functional activity of NRF2 is regulated by processes known as post-translational modifications such as phosphorylation, acetylation, and ubiquitination. Fyn kinases increase the stability of NRF2 and promote its nuclear accumulation. Acetylation also triggers transcriptional activation of NRF2 and potentiates the cellular antioxidant response. The nuclear factor erythroid 2-related factor 2 binding to AREs is mediated by NRF2-sMaf. This binding increases the specificity of NRF2 gene expression and allows the coordination of various metabolic pathways, including those involved in glutathione synthesis. Another unique feature of NRF2 is its feedback mechanism. The BTB and CNC homology 1 (BACH1) regulates and modulates the expression of genes that inhibit its activity. By regulating the feedback mechanism like BACH1, the NRF2 gene also prevents overactivation. Activation, regulation, and modulation of NRF2 are not limited to molecular interactions. Various environmental factors or chemical components contribute to the function of NRF2. Components such as sulforaphane and curcumin are photochemicals and have been reported to stimulate the activation of NRF2 and increase the expression of antioxidant genes.[12-20]

## MOLECULAR MECHANISMS OF NRF2 IN CANCER DEVELOPMENT

The NRF2 gene encodes a transcription factor that plays a crucial role in cellular defense mechanisms against oxidative stress and inflammation. Its involvement in cancer development is multifaceted, influencing various pathways that contribute to tumorigenesis, metastasis, and drug resistance. Understanding the molecular mechanisms of NRF2 in cancer is essential for developing targeted therapies and improving patient outcomes. The involvement of NRF2 in drug resistance is critical for the molecular development of cancer. This critical function stimulates anti-apoptotic protein molecules, allowing cancer cells to escape chemotherapy and promoting survival. For example, NRF2 activation in pancreatic cancer has been associated with increased resistance to gemcitabine, a widely used chemotherapeutic agent. This resistance is mediated by the upregulation of genes involved in detoxification and cell survival, highlighting the dual role of NRF2 as both tumor protector and

oncogene.[21] Signaling pathways interact with NRF2 in tumor development. In head and neck squamous cell carcinoma, it has been reported to cooperate with the NOTCH signaling pathway and promote malignant progression through the NRF2-GPX2-NOTCH3 axis. The NRF2 optimizes and modulates the activity of other transcription factors such as HIF1α, which is crucial for adaptive responses to hypoxia and contributes to the glycolytic phenotype of tumors.[22,23] Mutations in the NRF2 gene or genetic modifications in one of its co-modulator molecules, KEAP1, lead to abnormal morphological activation of NRF2. This morphology is implicated in various cancers. As a result of its structural biology, abnormal NRF2 induces uncontrolled growth, proliferation, and survival of cells. Epigenetic modifications also contribute to this complex functioning.[24]

## NRF2 AND ITS EFFECTS ON CANCER TREATMENT

Chemoresistance is a kind of resistance mechanism developed by cells against chemotherapy drug treatment, which is one of the traditional treatment methods. High expression levels of NRF2 accelerate the functioning and increase the levels of genes functionally involved in detoxification and antioxidant processes. The NRF2 transcriptional factor has been associated with poor prognosis in cancer types such as breast, colorectal, and pancreatic. The chemoresistance function of NRF2 was confirmed in a study on pancreatic cancer by its resistance to chemotherapeutic agents such as docetaxel and doxorubicin.[25,26]

The chemoresistance property of NRF2 has been an idea for the cancer treatment strategies developed. NRF2-targeted and sensitively developed chemotherapeutic agents can suppress NRF2 and act as inhibitors. One of the chemotherapeutic agents, brusatol, is an NRF2 inhibitor. Brusatol increases the sensitivity of pancreatic cancer cells to gemcitabine by down-regulating the activity of NRF2. Such approaches break the chemotherapeutic resistance mechanism of the NRF2 transcriptional factor and increase its sensitivity to chemotherapeutic agents.[27]

The NRF2 molecule is known to be involved in metabolic reprogramming. The physiological functioning of cancer cells, such as migration, invasion, energy demand, and survival, is related to cancer metabolism. The nuclear factor erythroid 2-related factor 2 is involved in the metabolic reprogramming of cancer cells by promoting pathways that support rapid growth and survival. It reorganizes the pentose-phosphate pathway provides substrates essential for cancer cells and reshapes the crucial metabolism of glucose and glutamine. Precisely targeted therapies inhibit NRF2 and thus target cancer metabolism.[28]

While NRF2 activation can protect normal cells from oxidative damage, long-term activation in cancer cells can promote tumor development and metastasis. The NRF2 is hypothesized to improve cancer cells' migratory and invasive characteristics by upregulating certain signaling pathways, such as the RhoA/ROCK pathway in breast cancer. This dual role makes therapeutic targeting of NRF2 difficult, as inhibiting its function may have unexpected implications for normal cellular processes.[25]

The NRF2 is typically activated in non-small cell lung cancer, which is often caused by KEAP1 gene alterations or direct NRF2 mutations. These mutations activate NRF2 constitutively, promoting cancer cell survival and resistance to chemotherapy. High NRF2 expression is associated with a bad prognosis in lung cancer patients, as it increases the expression of genes involved in detoxification and antioxidant defense, allowing cancer cells to tolerate oxidative stress from treatments.[29]

In breast cancer, NRF2 has been linked to tumor growth and metastasis. Elevated NRF2 levels have been linked to enhanced cell proliferation and migration, which contributes to the aggressive nature of certain breast cancer subtypes. The nuclear factor erythroid 2-related factor 2 activation can cause resistance to chemotherapeutic drugs, affecting therapy outcomes. According to research, inhibiting NRF2 may make breast cancer cells more susceptible to chemotherapy, opening up a new treatment route.[30]

The nuclear factor erythroid 2-related factor 2 has an important function in esophageal cancer by encouraging metabolic reprogramming and reducing ROS levels. According to studies, NRF2 activation promotes esophageal cancer cell growth and survival under oxidative stress. This

shows that NRF2 may be a target for therapeutic intervention in esophageal cancer.[31]

While cervical cancer, also known as cervical cancer, is caused by mutations or defects in KEAP1 as a result of genetic modifications, the silencing of molecules that function for the regulation of KEAP1 by epigenetic modifications also shows the cancer function of NRF2. Structural modification of NRF2 contributes to cell survival and meaningless proliferation in cancer cells and affects the phenotypic characterization of cancer-causing cells. In addition to existing therapies or as a refuge for palliative treatments, targeted therapy of NRF2 is a new idea that will pave the way for both personalized medicine and alternative modern medicine.[32]

The nuclear factor erythroid 2-related factor 2 has been reported as a poor prognosis in cancer types and derivatives. Resistance to chemotherapy in pancreatic cancer supports this phenomenon. Its activation in stellate cells, which are pancreatic cells, accelerates the tumorigenesis process as it functions to support the tumor microenvironment. When this is taken into account, targeted therapies become important. Precise-targeted therapies inhibit the activation of NRF2 and increase its sensitivity to chemotherapeutic agents.[33]

Glioblastoma, a cancerous form of glioblastoma, which is one of the cells of the neuronal network system and a cancer form of glial cells that usually provide nutrition and support to the cells of the nervous system, has been associated with the activation of NRF2. The nuclear factor erythroid 2-related factor 2 is known to inhibit cell proliferation and anti-apoptotic function of cancerous cells in glioblastoma. When the activation of NRF2 is blocked or inhibited, the growth of glioma cells is reduced in both *in vitro* and *in vivo* studies. This study demonstrates the functionality of NRF2 activation in glioma cells. Blocking the functioning of the NRF2 factor may slow and stop this aggressive form of cancer.[34]

The nuclear factor erythroid 2-related factor 2 activation in head and neck squamous cell carcinoma has been reported to play a role in tumor development and metastasis. It regulates the expression of genes associated with cell proliferation and survival, contributing to the aggressive nature of head and neck cancers. Silencing NRF2 or inhibiting its functioning will be effective in the treatment of head and neck squamous cell carcinomas.[35]

In conclusion, overexpression of the NRF2 transcriptional factor in case of defects or mutations that occur through genetic modifications has been reported to play a role in mechanisms such as meaningless proliferation, cell growth, survival, escape from apoptosis, which are processes of carcinogenesis or tumorigenesis. The nuclear factor erythroid 2-related factor 2, which is functional in various cancer derivatives or types, can develop resistance to chemotherapeutic agents, making it highly attractive for targeted therapies. In the future, pre-clinical and clinical studies in line with clinical findings will help to elucidate the molecular biology of cancer by targeting and inhibiting NRF2 in cancer research.

**Data Sharing Statement:** The data that support the findings of this study are available from the corresponding author upon reasonable request.

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## REFERENCES

1. Ohta T, Iijima K, Miyamoto M, Nakahara I, Tanaka H, Ohtsuji M, et ak. Loss of Keap1 function activates Nrf2 and provides advantages for lung cancer cell growth. Cancer Res 2008;68:1303-9. doi: 10.1158/0008-5472.CAN-07-5003.
2. Chan K, Han XD, Kan YW. An important function of Nrf2 in combating oxidative stress: Detoxification of acetaminophen. Proc Natl Acad Sci U S A 2001;98:4611-6. doi: 10.1073/pnas.081082098.
3. Erdogan MA, Nesil P, Altuntas I, Sirin C, Uyanikgil Y, Erbas O. Amelioration of propionic acid-induced autism spectrum disorder in rats through dapagliflozin: The role of IGF-1/IGFBP-3 and the Nrf2 antioxidant pathway. Neuroscience 2024;554:16-25. doi: 10.1016/j.neuroscience.2024.07.013.

4. Thai P, Statt S, Chen CH, Liang E, Campbell C, Wu R. Characterization of a novel long noncoding RNA, SCAL1, induced by cigarette smoke and elevated in lung cancer cell lines. Am J Respir Cell Mol Biol 2013;49:204-11. doi: 10.1165/rcmb.2013-0159RC.
5. Cescon DW, She D, Sakashita S, Zhu CQ, Pintilie M, Shepherd FA, et al. NRF2 pathway activation and adjuvant chemotherapy benefit in lung squamous cell carcinoma. Clin Cancer Res 2015;21:2499-505. doi: 10.1158/1078-0432.CCR-14-2206.
6. Solis LM, Behrens C, Dong W, Suraokar M, Ozburn NC, Moran CA, et al. Nrf2 and Keap1 abnormalities in non-small cell lung carcinoma and association with clinicopathologic features. Clin Cancer Res 2010;16:3743-53. doi: 10.1158/1078-0432.CCR-09-3352.
7. Nakamura BN, Lawson G, Chan JY, Banuelos J, Cortés MM, Hoang YD, et al. Knockout of the transcription factor NRF2 disrupts spermatogenesis in an age-dependent manner. Free Radic Biol Med 2010;49:1368-79. doi: 10.1016/j.freeradbiomed.2010.07.019.
8. Lim J, Ortiz L, Nakamura BN, Hoang YD, Banuelos J, Flores VN, et al. Effects of deletion of the transcription factor Nrf2 and benzo [a]pyrene treatment on ovarian follicles and ovarian surface epithelial cells in mice. Reprod Toxicol 2015;58:24-32. doi: 10.1016/j.reprotox.2015.07.080.
9. Lacher SE, Lee JS, Wang X, Campbell MR, Bell DA, Slattery M. Beyond antioxidant genes in the ancient Nrf2 regulatory network. Free Radic Biol Med 2015;88:452-65. doi: 10.1016/j.freeradbiomed.2015.06.044.
10. Fu J, Xiong Z, Huang C, Li J, Yang W, Han Y, et al. Hyperactivity of the transcription factor Nrf2 causes metabolic reprogramming in mouse esophagus. J Biol Chem 2019;294:327-40. doi: 10.1074/jbc.RA118.005963.
11. Kaspar JW, Jaiswal AK. Tyrosine phosphorylation controls nuclear export of Fyn, allowing Nrf2 activation of cytoprotective gene expression. FASEB J 2011;25:1076-87. doi: 10.1096/fj.10-171553.
12. Gan L, Johnson DA, Johnson JA. Keap1-Nrf2 activation in the presence and absence of DJ-1. Eur J Neurosci 2010;31:967-77. doi: 10.1111/j.1460-9568.2010.07138.x.
13. Kobayashi EH, Suzuki T, Funayama R, Nagashima T, Hayashi M, Sekine H, et al. Nrf2 suppresses macrophage inflammatory response by blocking proinflammatory cytokine transcription. Nat Commun 2016;7:11624. doi: 10.1038/ncomms11624.
14. Ştefanache T, Forna N, Bădescu M, Jitaru D, Dragos ML, Rezuş C, et al. Modulation of the activity of certain genes involved in tumor cell metabolism in the presence of the cytotoxic peptides defensin and cathelicidin LL37. Exp Ther Med 2019;18:5033-40. doi: 10.3892/etm.2019.8117.
15. Nguyen VT, Fuse Y, Tamaoki J, Akiyama SI, Muratani M, Tamaru Y, et al. Conservation of the Nrf2-mediated gene regulation of proteasome subunits and glucose metabolism in zebrafish. Oxid Med Cell Longev 2016;2016:5720574. doi: 10.1155/2016/5720574.
16. Hirotsu Y, Katsuoka F, Funayama R, Nagashima T, Nishida Y, Nakayama K, et al. Nrf2-MafG heterodimers contribute globally to antioxidant and metabolic networks. Nucleic Acids Res 2012;40:10228-39. doi: 10.1093/nar/gks827.
17. Chartoumpekis DV, Ziros PG, Zaravinos A, Iskrenova RP, Psyrogiannis AI, Kyriazopoulou VE, et al. Hepatic gene expression profiling in Nrf2 knockout mice after long-term high-fat diet-induced obesity. Oxid Med Cell Longev 2013;2013:340731. doi: 10.1155/2013/340731.
18. Thangasamy A, Rogge J, Krishnegowda NK, Freeman JW, Ammanamanchi S. Novel function of transcription factor Nrf2 as an inhibitor of RON tyrosine kinase receptor-mediated cancer cell invasion. J Biol Chem 2011;286:32115-22. doi: 10.1074/jbc.M111.245746.
19. Jyrkkänen HK, Kuosmanen S, Heinäniemi M, Laitinen H, Kansanen E, Mella-Aho E, et al. Novel insights into the regulation of antioxidant-response-element-mediated gene expression by electrophiles: Induction of the transcriptional repressor BACH1 by Nrf2. Biochem J 2011;440:167-74. doi: 10.1042/BJ20110526.
20. Wu KC, Cui JY, Klaassen CD. Beneficial role of Nrf2 in regulating NADPH generation and consumption. Toxicol Sci 2011;123:590-600. doi: 10.1093/toxsci/kfr183.
21. Sun X, Dong M, Li J, Sun Y, Gao Y, Wang Y, et al. NRF2 promotes radiation resistance by cooperating with TOPBP1 to activate the ATR-CHK1 signaling pathway. Theranostics 2024;14:681-98. doi: 10.7150/thno.88899.
22. Lin L, Wu Q, Lu F, Lei J, Zhou Y, Liu Y, et al. Nrf2 signaling pathway: Current status and potential therapeutic targetable role in human cancers. Front Oncol 2023;13:1184079. doi: 10.3389/fonc.2023.1184079.
23. Kim TH, Hur EG, Kang SJ, Kim JA, Thapa D, Lee YM, et al. NRF2 blockade suppresses colon tumor angiogenesis by inhibiting hypoxia-induced activation of HIF-1α. Cancer Res 2011;71:2260-75. doi: 10.1158/0008-5472.CAN-10-3007.
24. Saigusa D, Motoike IN, Saito S, Zorzi M, Aoki Y, Kitamura H, et al. Impacts of NRF2 activation in non-small-cell lung cancer cell lines on extracellular metabolites. Cancer Sci 2020;111:667-78. doi: 10.1111/cas.14278.
25. Zhang C, Wang HJ, Bao QC, Wang L, Guo TK, Chen WL, et al. NRF2 promotes breast cancer cell proliferation and metastasis by increasing RhoA/ROCK pathway signal transduction. Oncotarget 2016;7:73593-606. doi: 10.18632/oncotarget.12435.

26. Zhang P, Singh A, Yegnasubramanian S, Esopi D, Kombairaju P, Bodas M, et al. Loss of Kelch-like ECH-associated protein 1 function in prostate cancer cells causes chemoresistance and radioresistance and promotes tumor growth. Mol Cancer Ther 2010;9:336-46. doi: 10.1158/1535-7163.MCT-09-0589.
27. Xiang Y, Ye W, Huang C, Yu D, Chen H, Deng T, et al. Brusatol enhances the chemotherapy efficacy of gemcitabine in pancreatic cancer via the Nrf2 signalling pathway. Oxid Med Cell Longev 2018;2018:2360427. doi: 10.1155/2018/2360427.
28. Zhang Y, Xin Z, Dong B, Xue W. Combination of the NRF2 inhibitor and autophagy inhibitor significantly inhibited tumorigenicity of castration-resistant prostate cancer. Comput Math Methods Med 2022;2022:4182401. doi: 10.1155/2022/4182401.
29. Wang Q, Xu L, Wang G, Chen L, Li C, Jiang X, et al. Prognostic and clinicopathological significance of NRF2 expression in non-small cell lung cancer: A meta-analysis. PLoS One 2020;15:e0241241. doi: 10.1371/journal.pone.0241241.
30 Kitano Y, Baba Y, Nakagawa S, Miyake K, Iwatsuki M, Ishimoto T, et al. Nrf2 promotes oesophageal cancer cell proliferation via metabolic reprogramming and detoxification of reactive oxygen species. J Pathol 2018;244:346-57. doi: 10.1002/path.5021.
31. Bauer AK, Cho HY, Miller-Degraff L, Walker C, Helms K, Fostel J, et al. Targeted deletion of Nrf2 reduces urethane-induced lung tumor development in mice. PLoS One 2011;6:e26590. doi: 10.1371/journal.pone.0026590.
32. Liao H, Zhu D, Bai M, Chen H, Yan S, Yu J, et al. Stigmasterol sensitizes endometrial cancer cells to chemotherapy by repressing Nrf2 signal pathway. Cancer Cell Int 2020;20:480. doi: 10.1186/s12935-020-01470-x.
33. Ryoo IG, Choi BH, Kwak MK. Activation of NRF2 by p62 and proteasome reduction in sphere-forming breast carcinoma cells. Oncotarget 2015;6:8167-84. doi: 10.18632/oncotarget.3047.
34. Gall Trošelj K, Tomljanović M, Jaganjac M, Matijević Glavan T, Čipak Gašparović A, Milković L, et al. Oxidative stress and cancer heterogeneity orchestrate NRF2 roles relevant for therapy response. Molecules 2022;27:1468.
35. Cloer EW, Goldfarb D, Schrank TP, Weissman BE, Major MB. NRF2 activation in cancer: From DNA to protein. Cancer Res 2019;79:889-98. doi: 10.1158/0008-5472.CAN-18-2723.