

Review

The FN3K-Nrf2 Axis: A Novel Therapeutic Target in Cancer Metabolism

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Abstract

Fructosamine-3-kinase (FN3K) is crucial for cellular metabolism, reversing early glycation products to maintain protein function and cellular homeostasis. Recent research highlights FN3K's role in cancer biology through its interaction with the Nrf2 transcription factor, which regulates cellular antioxidant responses and redox homeostasis. FN3K's deglycation activity can influence Nrf2 function, impacting cancer development and progression. Evidence suggests that FN3K stabilizes Nrf2, promoting the expression of genes involved in cell survival, proliferation, and chemotherapy resistance. Increased FN3K expression in cancers is linked to poor prognosis and treatment resistance, possibly by preventing Nrf2 ubiquitination and degradation. This sustained activation of Nrf2 target genes helps cancer cells bolster their antioxidant defenses and support tumor growth. Understanding the FN3K-Nrf2 interaction offers new therapeutic opportunities. Targeting FN3K-mediated deglycation could modulate Nrf2 activity in cancer, potentially enhancing treatment efficacy and reducing resistance. Further research is needed to clarify the molecular mechanisms and develop specific inhibitors targeting FN3K in cancer cells. This review aims to provide an overview of FN3K, emphasize its importance in deglycation, and discuss pharmaceutical interventions targeting FN3K to combat cancer.

Keywords: Fructosamine-3-kinase (FN3K), nuclear factor erythroid 2-related factor-2 (Nrf2), deglycation, oncogenic, cancer

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Cancer remains a major global health issue, ranking among the leading causes of morbidity and mortality worldwide. Despite significant research and advancements in understanding cancer biology and treatment, it continues to be a formidable challenge due to its complexity and the diversity of tumor types. ^[1] Traditional therapies—surgery, chemotherapy, and radiation—while somewhat effective, often suffer from significant limitations such as toxicity, resistance, and lack of specificity, leading to adverse effects and relapse. ^[2] Recent breakthroughs in molecular

biology and genetics have facilitated the development of novel cancer therapies, particularly targeted treatments that leverage specific molecular abnormalities inherent to cancer cells. ^[3] Targeted therapies, including tyrosine kinase inhibitors and immune checkpoint inhibitors, have transformed cancer treatment by providing greater specificity and efficacy than conventional therapies. However, the emergence of resistance and the limited scope of these treatments highlight the need for ongoing research into new therapeutic targets and strategies. ^[4]

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A promising area of cancer research involves targeting metabolic pathways specific to cancer cells. These cells exhibit unique metabolic alterations, such as the Warburg effect, which supports their rapid proliferation and ability to survive under adverse conditions.^[5,6] Targeting metabolic enzymes and pathways unique to cancer cells could selectively impair their growth while minimizing harm to normal cells.^[7] Among the various metabolic targets, fructosamine-3-kinase (FN3K) has attracted attention for its role in the deglycation process. FN3K catalyzes the phosphorylation of fructosamines on proteins, forming fructosamine-3-phosphate, which is then hydrolyzed to glucose and the corresponding amino acid. This process is vital in preventing the accumulation of advanced glycation end products (AGEs), which have been implicated in numerous pathological conditions, including cancer.^[8,9] Emerging evidence suggests that FN3K is crucial in different aspects of cancer biology. Its overexpression in certain cancers indicates a potential link between FN3K activity and tumorigenesis, making it a promising target for therapeutic intervention.^[10]

Sanghvi et al. demonstrated that the oncogenic function of nuclear factor erythroid 2-related factor-2 (Nrf2), a transcription activator involved in cellular stress response, depends on the deglycation process mediated by FN3K.^[11] Nrf2 is a key transcription factor that defends against oxidative stress and regulates cytoprotective genes, but its high expression in cancer may lead to treatment resistance, highlighting its potential as a therapeutic target.^[12] Further research confirmed that the glycated state of Nrf2 promotes the prognosis and progression of liver and lung cancer in experimental models lacking the FN3K gene.^[11] FN3Ks are linked to redox regulation and NAD metabolism, making them promising therapeutic targets for metabolic disorders and diabetic complications by mitigating harmful effects of glycated glucose through deglycation.^[13-15] However, FN3K's involvement in cancer progression, particularly through the direct upregulation of Nrf2 levels in cancer cells, has been highlighted in an extensive study, which demonstrated that anti-cancer drugs, such as oxaliplatin, modulate the mRNA expression levels of FN3K. This modulation results in a decreased Nrf2 response and suppression of antioxidant response elements (ARE) genes, thereby enhancing cancer cell sensitivity to treatment.^[10] Nrf2 plays a crucial role in mediating antioxidant responses; however, its hyperactivation in cancer cells contributes to enhanced survival and chemoresistance, indicating its potential as a target for improving the efficacy of chemotherapy.^[16] Yousefi et al. reported reduced FN3K enzyme activity in breast cancer tissues, suggesting this reduction may aid cancer cell survival and disease progression. These findings suggest that FN3K activity could serve as a potential biomarker for breast cancer diagnosis and prognosis.^[17] In colorectal cancer, higher FN3K expression levels correlate with advanced tumor stages and poor prognosis for patients.^[18] Preclinical studies have shown that inhibiting FN3K can reduce tumor growth and enhance cancer cells' sensitivity to conventional therapies.^[10] Furthermore, the ability to selectively target cancer cells while sparing normal cells provides a significant advantage by reducing potential adverse effects.^[19]

Fructosamine-3-Kinase (FN3K) Enzyme

Embracing the Structural Revelations

Fructosamine-3-kinases (FN3Ks) are a conserved group of deglycation enzymes responsible for removing ribose and fructose sugars from lysine residues (ketosamines) on protein surfaces.^[20] FN3K is part of the GHMP kinase family, which includes galactokinase, homoserine kinase, mevalonate kinase, and phosphomevalonate kinase.^[21] The FN3K protein is a 35-kDa monomer composed of 309 amino acids and does not show significant similarity to other known proteins. Homology searches and sequence analyses using electron spray ionization-tandem mass spectrometry (ESI-LC/MS/MS) revealed that its genomic sequences bear similarities to those on human chromosomes 1 and 17.^[22] The structure of FN3K includes several key regions: the N-terminal domain, the central catalytic domain, and the C-terminal domain.^[23] The central catalytic domain is the most critical part, containing the active site responsible for the enzyme's activity. The ATP binding loop, which is conserved across various organisms, contains a disulfide bond that functions as a redox switch regulating the enzyme's activity.^[10,24] The crystal structure of HsFN3K reveals that its loop extension (116–138) is not essential for kinase activity, it primarily exists as a monomer with lower redox sensitivity than plant FN3Ks, and specific residues critical for deglycation have been identified.^[25] The C-terminal domain contributes to the structural integrity and proper folding of FN3K, often playing a role in substrate specificity and recognition to ensure correct interaction with the fructosamine substrate.^[11,24]

FN3K: Unlocking the Power of Deglycation

The intricate structure of fructosamine-3-kinase (FN3K) provides insights into its function and mechanism of action. The enzyme's specificity for fructosamine substrates is dictated by the unique architecture of its active site, which accommodates these modified proteins and facilitates their phosphorylation.^[22] This specificity ensures the selective binding and phosphorylation of fructosamines by FN3K, thereby preventing the accumulation of advanced glycation end products (AGEs). This selectivity is vital for its role in deglycation and for potential therapeutic targeting.^[23] Understanding FN3K's structure paves the way for designing specific inhibitors that can bind to the active site or regulatory regions of the enzyme, potentially modulating FN3K activity in diseases like cancer, where altered deglycation processes contribute to disease progression.^[10] The role of FN3K in deglycation was demonstrated in a study where erythrocytes incubated in a glucose-containing medium exhibited accumulation of glycated hemoglobin. Increased levels of glycated hemoglobin were detected in the pres-

ence of 1-deoxy-1-morpholinofructose (DMF), a cell-permeable inhibitor of FN3K.^[24] The deglycation process involves transferring the gamma phosphate from adenosine triphosphate (ATP) to the 3' hydroxyl group in the ketosamine substrate, forming fructoselysine-3-phosphate (FL3P).^[26,27]

Proton nuclear magnetic resonance (NMR) studies, which couple ¹H and ³¹P, confirmed that the deglycation process involves the phosphorylation of fructosamine residues at the third carbon of the fructose moiety.^[22] The reactivity of FL3P, due to the proximity of the keto and phosphate groups, increases its susceptibility to degradation via β -elimination. This degradation results in a rapid decline in FL3P concentration, with a half-life of 5-6 hours, followed by an increase in 3-deoxyglucosone (3-DG) levels due to the β -elimination of FL3P.^[23] 3-DG, a potent glycating agent, inhibits enzyme activity and cell growth and contributes to diabetic embryopathy.^[22,23] Polymerase chain reaction (PCR) studies have shown a strong correlation between the abundance of the FN3K enzyme and the extent of glycation in various mammalian tissues, particularly in the heart, nerves, and lungs, which are more prone to glycation.^[22,28] For the FN3K-deglycation system to function optimally, cells or tissues must have enzymes that convert 3-DG into inactive metabolites, such as 3-deoxy fructose or 3-deoxy-2-ketogluconic acid, in conjunction with FN3K.^[22] The specificity for glycated proteins is demonstrated by lower Michaelis constant (*K_m*) values for histone-bound fructose lysine residues compared to free fructose and fructose lysines.^[22]

Evolutionarily, the fructosamine 3 kinase (FN3K) gene has been conserved across generations. While simple eukaryotic and prokaryotic species possess a single gene copy, more complex eukaryotes such as mammals have two copies: FN3K and FN3K-related protein (FN3KRP).^[22,28] FN3KRP plays a crucial role in the deglycation of ribulosamines and psicosamines, which are intermediates in the ribose 5-phosphate and Calvin cycles. FN3KRP specifically catalyzes the phosphorylation of low-molecular-mass and protein-bound ribulosamines and psicosamines, while excluding fructosamines.^[14] The glycation and deglycation mechanisms are represented in Figures 1(a) and 1(b), respectively.

Uncovering the Efficiency Gaps

Fructosamine-3-kinase (FN3K) plays a crucial role in maintaining the balance between glycation and deglycation.^[29] Glycation involves the covalent modification of proteins through the attachment of reducing sugars, resulting in the formation of Amadori products, which can further transform into advanced glycation end products (AGEs) associ-

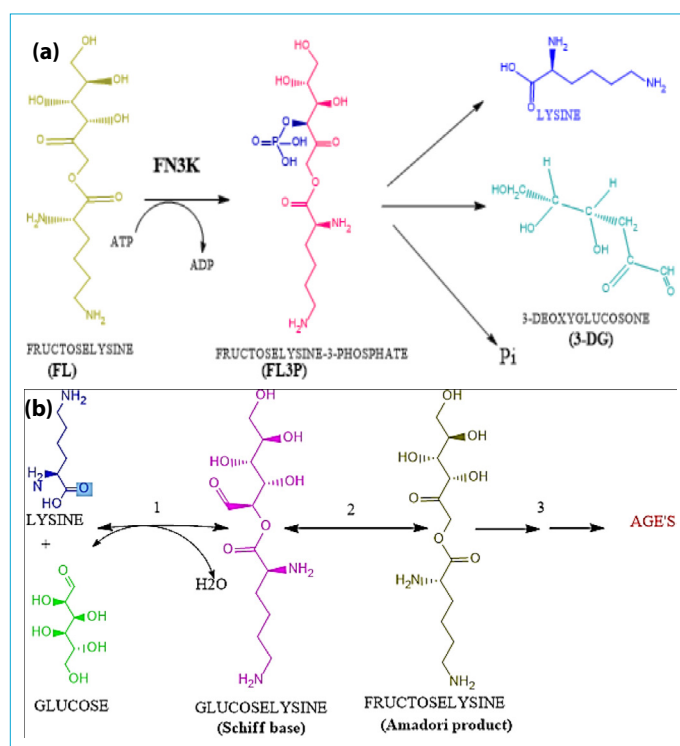


Figure 1. (a) Non-enzymatic glycation (Maillard reaction).

Step 1: Addition of Glucose (Sugar) and Lysine (Amine) resulting in formation of Schiff base (Glucose lysine). Step 2: Rearrangement resulting in formation of Amadori product. Step 3: Formation of Advanced Glycation End products (AGE's).

(b) Enzymatic Deglycation by Fructosamine-3-kinase.

Phosphorylation of FL, thus forming FL3P which further destabilizes and spontaneously decomposes into Lysine, inorganic phosphate (Pi) and 3-Deoxyglucosone (3-DG).

ated with various diseases, including diabetes and cancer.^[30,31] FN3K catalyzes the phosphorylation of fructosamines, facilitating their removal and preventing the accumulation of AGEs. Homeothermic animals have evolved the deglycation process to counteract the adverse effects of AGEs.^[27] AGEs significantly contribute to the cross-linking of proteins, alterations in molecular conformation, and changes in receptor recognition and biological activity.^[32,33] FN3K acts as a protein-repair enzyme, restoring the original, unmodified lysine residues that are involved in the glycation process during deglycation.^[34] Proper cellular function depends on FN3K activity, and dysregulated FN3K activity can disturb cellular equilibrium, potentially leading to pathological conditions. Uncontrolled deglycation of the nuclear transcription factor Nrf2 is associated with tumor proliferation and the emergence of resistance to cancer therapies.^[11] Therefore, the precise regulation of FN3K activity is crucial for maintaining cellular homeostasis.^[8] The clinical implications associated with AGEs are depicted in Figure 2.

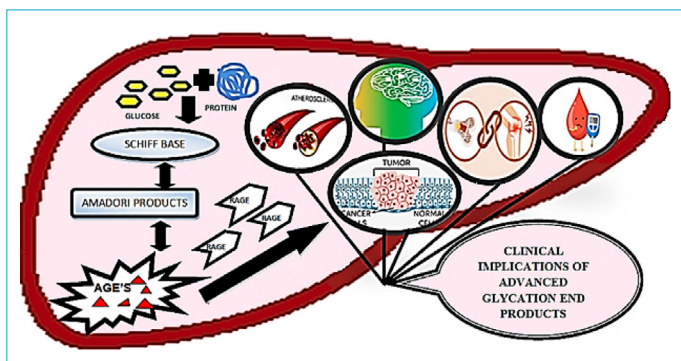


Figure 2. Glycation or Maillard reaction: Formation of AGE's which on binding to RAGE's are responsible for clinical implications such as Atherosclerosis, Alzheimer's condition, and Diabetes, Arthritis, Tumor and Cancer development.

FN3K: A Key Player in Cancer Progression

Cancer progression involves a series of intricate biological processes, including alterations in cellular metabolism, proliferation, survival, and interactions with the tumor microenvironment.^[35] Recent research indicates that fructosamine-3-kinase (FN3K) plays a significant role in these processes. FN3K is an enzyme recognized for its function in removing fructosamines to prevent the formation of advanced glycation end products (AGEs).^[8,10]

Several mechanisms through which FN3K influences cancer progression include:

Regulation of Protein Function: Glycation can impair protein function by modifying its structure and stability. FN3K helps maintain protein homeostasis by removing these modifications, ensuring that proteins retain their normal function.^[31,36] AGEs can form cross-links with other proteins, leading to the aggregation of proteins.^[32,33] FN3K's deglycation activity prevents this accumulation, protecting cells from the adverse effects of AGEs.^[13] AGEs are also known to induce oxidative stress by generating reactive oxygen species (ROS). FN3K's role in reducing AGE levels indirectly helps alleviate oxidative stress, thus protecting proteins and other cellular components.^[37]

Modulation of Extracellular Matrix (ECM) Remodeling:

The ECM plays a vital role in the invasion, dissemination, and angiogenesis of cancer cells.^[38] Glycation can alter the properties of ECM proteins, hindering their breakdown and restructuring. FN3K's role in reversing glycation on ECM proteins is crucial for maintaining the integrity and functionality of the ECM. By modulating ECM glycation, FN3K can influence tumor invasion and metastasis.^[39]

Nrf2-FN3K Antioxidant Alliance

Nuclear Factor Erythroid 2-Related Factor 2 (Nrf2)

The regulation of Nrf2 activity and its cytosolic concentrations is governed by a tightly controlled cycle of synthesis and degradation.^[40] In humans, the nuclear factor erythroid-derived 2-like 2 gene (NFE2L2) encodes the nuclear factor erythroid 2-related factor 2 (Nrf2), a protein characterized by a basic leucine zipper (bZIP) structure that plays a critical role in regulating the expression of antioxidant proteins, thereby providing defense against oxidative damage and inflammation.^[11] Nrf2 features a Cap 'n' Collar (CNC) motif and contains seven highly conserved domains (Neh), each with distinct functions^[41] (Fig. 3). The small musculoaponeurotic fibrosarcoma (sMaf) proteins—MafF, MafG, and MafK—can form heterodimers with Nrf2 through its Neh1 domain, which possesses a CNC-bZIP configuration.^[42,43] Nrf2 levels are tightly regulated by the inhibitory action of Keap1, which forms complexes with the DLG and ETGE motifs located in the Neh2 domain.^[44] The Neh3-5 domains interact with components of the transcriptional machinery and act as transactivation domains, enhancing the overall efficacy of Nrf2. The Neh6 domain may contain a degron that is involved in the redox-insensitive degradation of Nrf2. Moreover, the Neh7 domain is thought to regulate Nrf2 transcriptional activity through physical interaction with the retinoid X receptor.^[45,46]

The regulation of the Nrf2 transcription factor in the cytosol is mainly controlled through its interaction with the Kelch-like ECH-associated protein 1 (Keap1), particularly via the DLG and ETGE motifs of Nrf2 (Fig. 4).^[47]

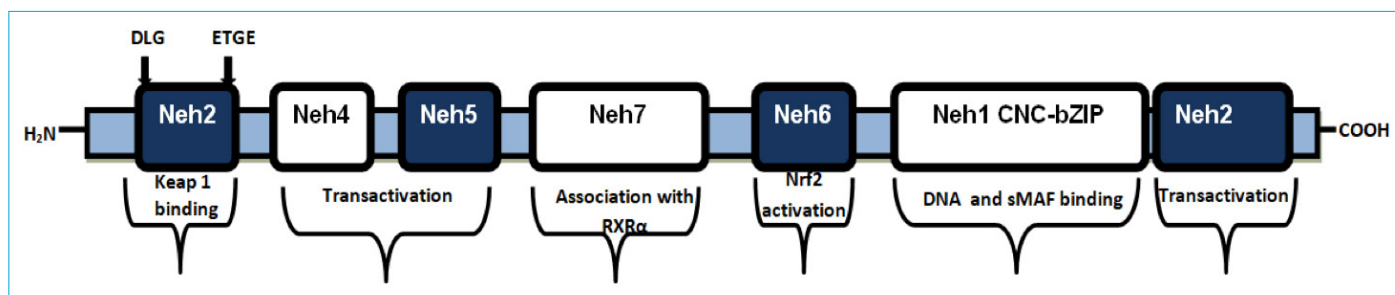


Figure 3. Schematic structural representations of Neh 1-7 domains of Nrf2-transcription factor.

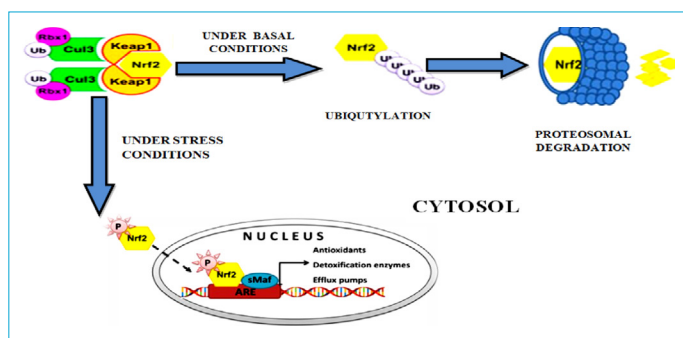


Figure 4. Regulation of Nrf2 via Keap1-Cullin3-E3 Ligase complex under Basal and stress condition.

(a) Under homeostatic conditions Keap 1 interacts with Nrf2 in the cytosol resulting in polyubiquitylation and subsequent proteasomal degradation resulting in minimal or absence of Nrf2 activation; (b) Under stress conditions the binding of Keap1 to Nrf2 is impaired, thus resulting in free release of Nrf2 in the cytosol followed by its translocation into the nucleus wherein it interacts with small MAF proteins and ARE proteins.

Keap1 serves as an adaptor for Cullin3 and RBX1 proteins, forming an E3 ligase complex that ubiquitinates Nrf2, leading to its degradation via the 26S proteasome.^[48] Under conditions of oxidative stress, conformational changes in the cysteine residues of Keap1 (27 cysteine residues in humans and 25 in mice) facilitate the release of the Nrf2 transcription factor.^[49-51] This liberated Nrf2 translocates to the nucleus, where it executes its antioxidant function by heterodimerizing with small Maf proteins (sMAFs), binding to antioxidant response elements (ARE), and upregulating enzymes involved in metabolic pathways, including Phase I and Phase II detoxification enzymes.^[52,53]

Janus Effect of Nrf2

Nrf2 is a transcription factor that orchestrates both basal and stress-inducible activation of a diverse array of cytoprotective genes, thus maintaining homeostatic balance.^[54] Under normal physiological conditions, Nrf2 exerts its antioxidant function while its cytosolic levels are regulated through ubiquitination and proteasomal degradation in complex with the Keap1 inhibitor. In hypoxic and stressful environments, Nrf2 expression is elevated, enhancing its cytoprotective antioxidant activity and facilitating beneficial cellular growth.^[55]

However, this enhanced activity may also facilitate the proliferation of cancerous cells, contributing to resistance against cancer therapies.^[56,57] The Nrf2-Keap1 signaling pathway is crucial for regulating oxidative stress and responding to toxic metal exposure, with Nrf2 providing protection while its prolonged activation may contribute to carcinogenesis, necessitating further investigation.^[58]

Consequently, pharmacological activation of Nrf2 is regarded as a promising therapeutic strategy for various chronic diseases characterized by oxidative stress and inflammation, including neurodegenerative, cardiovascular, and metabolic disorders.^[59,60] Focusing on the Nrf2 pathway presents a promising approach to address drug resistance and tumorigenesis driven by cancer stem cells in pancreatic ductal adenocarcinomas, potentially enhancing treatment efficacy.^[61] Nrf2-dependent functions offers a dual therapeutic approach for Ewing sarcoma, potentially inhibiting metastasis at low EWSR1-FLI1 levels and overcoming treatment challenges at high levels, improving patient outcomes.^[62] Targeting Nrf2 offers a promising approach for Th17-dependent autoimmune diseases and novel cancer therapies by modulating immune function, redox balance, and disrupting cancer cell survival mechanisms.^[63,64] In the context of cancer, however, the role of Nrf2 is more intricate; its activation can confer a survival advantage to tumors, making its inhibition preferable. Thus, Nrf2 operates as a double-edged sword: its regulated levels promote the growth and maintenance of healthy cells, while also providing cancer cells with enhanced survival capabilities, resulting in resistance to chemotherapy and radiation, as well as impeding apoptosis pathways, as depicted in Figure 5.^[65-67] Nrf2 plays a dual role in colorectal cancer by protecting against oxidative stress and promoting cancer progression, influencing ferroptosis and chemotherapy resistance, with potential modulators explored for treatment.^[68] Given the physiological significance of Nrf2, numerous studies have concentrated on the development of synthetic and plant-derived compounds that can act as either activators or inhibitors of Nrf2.^[69,70]

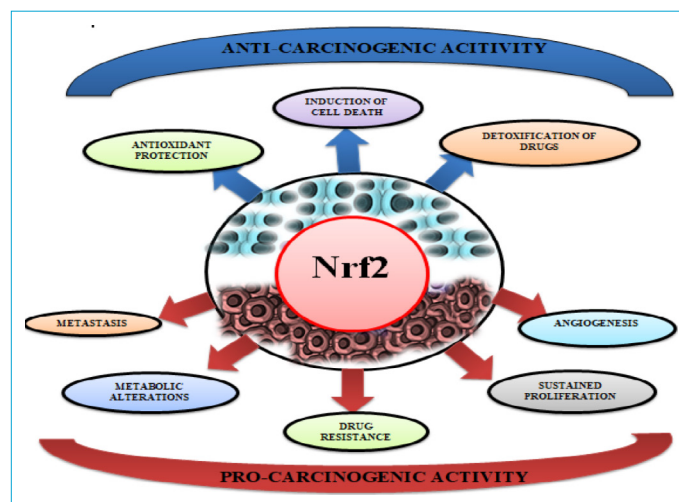


Figure 5. Schematic diagram representing the Janus effect of Nrf2, supporting the anti-carcinogenic and pro-carcinogenic activities.

The Regulatory Agents- Nrf2 Inhibitors

Nrf2 regulates redox balance and antioxidant enzyme levels, but its overexpression in cancer promotes tumor growth, invasion, and chemoresistance. Targeting Nrf2 may enhance therapeutic efficacy in cancer treatment.^[71] A range of small molecules are recognized for their capacity to inhibit Nrf2 function through various mechanisms. Nuclear receptor ligands, such as dexamethasone and clo-betasol propionate, negatively regulate Nrf2's transcriptional activity.^[72-74] Ascorbic acid is particularly notable for restoring the sensitivity of cancer cells to pharmacological agents by interacting with RAR α , thereby limiting Nrf2's binding to the antioxidant response element (ARE).^[69,75] All-trans-retinoic acid and bexarotene, acting as agonists for the retinoic acid receptor- α (RAR α) and retinoid X receptor- α , respectively, inhibit Nrf2 transcriptional activity by forming complexes with Nrf2, which prevents the Nrf2 α complexes from binding to the ARE.^[59,74,76]

The natural quassinoid brusatol and flavonoids such as luteolin and wogonin are well-documented for their ability to suppress Nrf2 levels and associated proteins, thereby diminishing cancer cells' resistance to treatment.^[72,77-79] Additionally, the mycotoxin ochratoxin A and the naturally occurring coffee alkaloid trigonelline effectively inhibit Nrf2's nuclear translocation.^[57,59,80] Other inhibitors, including chrysin, apigenin, oridonin, and parthenolide, target Nrf2 through the phosphoinositide 3-kinase/protein kinase B (PI3K/Akt), peroxisome proliferator-activated receptor γ (PPAR γ), nuclear factor kappa B (NF- κ B), and Janus kinase/signal transducer and activator of transcription (JNK-STAT) pathways.^[75,81-83] Oxaliplatin promotes ferroptosis and oxidative stress in colorectal cancer cells by inhibiting the Nrf2 signaling pathway, thereby augmenting the efficacy of ferroptosis inducers, such as erastin, and decreasing cell viability.^[84] Co-administration of brusatol, an Nrf2 inhibitor, with low-dose oxaliplatin significantly enhances chemosensitivity in breast cancer, resulting in reduced cell migration and proliferation, while also lowering the effective dose of oxaliplatin.^[85] Amiloride has been reported to increase sunitinib sensitivity in renal cell carcinoma by modulating FN3K and VEGFR2, thus inducing synergistic cytotoxic effects and overcoming resistance mechanisms in cancer cells.^[86] The commonly used inhibitors of Nrf2 are illustrated in Figure 6.

Interplay between Nrf2 and Glycation in Cancers

The interaction between Nrf2 and glycation is significant in the context of cancer. Activation of Nrf2 can mitigate glycation-induced oxidative stress by upregulating antioxidant defenses and detoxifying enzymes, potentially inhibiting the formation and accumulation of advanced glycation end-products (AGEs).^[87] However, in cancer cells, chronic

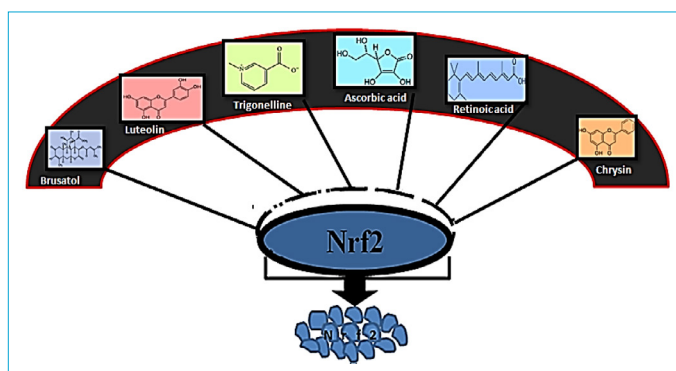


Figure 6. Commonly used Inhibitors of Nrf2-transcription factor.

activation of Nrf2 can elicit an adaptive response that promotes cell survival and proliferation despite elevated levels of oxidative stress and glycation.^[88] Furthermore, the relationship between Nrf2 and the AGE-RAGE axis can affect cancer progression. Activation of Nrf2 can mitigate AGE-induced oxidative stress and inflammation; however, persistent Nrf2 activation in cancer cells may foster a pro-survival phenotype, thereby enhancing resistance to chemotherapy and facilitating tumor growth.^[52,56,89,90] Therefore, targeting the Nrf2 pathway and the processes associated with glycation may provide promising therapeutic strategies for cancer treatment.^[91]

Increased activation of Nrf2 is frequently observed in proliferating cancer cells due to mutations across various malignancies, including liver, lung, head and neck, bladder, and pancreatic cancers.^[92,93] Nrf2 serves as a crucial oncogene that drives the process of oncogenesis.^[94] Somatic mutations affecting glycation sites on Nrf2, such as R499W, R569C, and R569H, are infrequent but are found in significant malignancies like endometrial carcinoma, colorectal carcinoma, and melanoma.^[8,11] Fructosamine-3-kinase (FN3K), which deglycates Nrf2 through the phosphorylation of lysine and arginine residues, enhances Nrf2 activity in hepatocellular carcinoma cells, thereby providing antioxidant protection.^[95] Targeting FN3K with small molecule inhibitors presents a promising strategy for cancer treatment.^[10] Nrf2 inhibitors have demonstrated effectiveness in slowing the progression of breast cancer.^[96] Maintaining Nrf2 in its glycated form by inhibiting FN3K activity may be a critical approach for developing therapeutic agents from either synthetic or natural sources.^[8,10] Rational drug design employing molecular docking, virtual screening, and molecular dynamics can expedite the identification of anticancer compounds targeting various oncogenic proteins involved in oncogenesis.^[10] This strategy enhances the development of more effective drug candidates. Given that many malignancies exhibit altered oncogenic pathways, kinase modulators can be utilized as antineoplastic agents to impede cancer progression.^[97]

From Vision to Reality: The Requirement for the Development of FN3K Inhibitors

PCR studies have established the presence of FN3K in nearly all mammalian tissues, including the sciatic nerves of rats and humans, bovine vagal nerves, bovine retinas, pancreases, rat hearts, and human erythrocytes, with a notable abundance in kidney tissues.^[22,28] Evidence supporting FN3K's role in the deglycation process is provided by animal studies demonstrating that FN3K-knockout mice exhibited elevated protein glycation.^[29] FN3K is a distinctive enzyme that facilitates deglycation by phosphorylating key amino acids such as lysine and arginine in Nrf2, thereby increasing Nrf2 levels within the cytosol.^[8,98] Research has emphasized FN3K's role in activating the oncogenic properties of Nrf2.^[11] The development of small kinase inhibitors targeting Nrf2-driven cancers is justified by the observation that approximately 30% of cancer cases involve mutational activation of Nrf2, given its widespread presence in nearly all tissues.^[99] The characteristic phenotype of FN3K knockout mice, which display increased protein glycation despite reduced FN3K levels, suggests that FN3K inhibitors are likely to be well-tolerated in the body.^[29] FN3K inhibitors possess the potential to function as therapeutic agents by modulating the enzymatic activity of FN3K (Fig. 7).^[8] When FN3K is inactive, it maintains oncogenic Nrf2 in a glycosylated state, rendering it inactive. Therefore, inhibiting FN3K could promote the formation of glycosylated Nrf2, representing a promising strategy in cancer treatment.^[8,10] Recent virtual screening studies have validated the *in vitro* efficacy of anticancer drugs against the FN3K target, resulting in the downregulation of Nrf2 levels as well as associated antioxidant-responsive elements and proteins.^[10] However, *in vivo* studies are required to corroborate the *in vitro* findings regarding the efficacy of these anticancer agents in modulating FN3K activity. Consequently, the development of a potent small molecule inhibitor targeting FN3K is a novel undertaking that enhances our understand-

ing of its role in tumorigenesis and advances the field of pharmacological agents.^[8]

Conclusion

The intricate relationship between the FN3K enzyme and Nrf2 in cancer biology has emerged as a critical area of investigation, illuminating the complex molecular dynamics that drive tumor progression. The FN3K enzyme serves a pivotal role in enhancing the oncogenic potential of Nrf2 through its deglycation activity, which modifies Nrf2 in a way that promotes its stability and activity. While Nrf2 is traditionally recognized for its protective role against oxidative stress, it has the potential to become an oncogenic driver when hyper-activated. This hyper-activation allows Nrf2 to contribute to essential processes such as cancer cell survival, proliferation, and metastasis, thereby fueling tumor growth.

The deglycation process mediated by FN3K not only stabilizes Nrf2 but also leads to a continuous activation of its downstream signaling pathways. This persistent antioxidant response effectively supports the malignant behavior of cancer cells, allowing them to thrive in adverse conditions. By providing a robust defense mechanism against oxidative stress, which typically acts to suppress tumor development, the FN3K-Nrf2 axis has been identified as a crucial contributor to cancer pathogenesis. This identification highlights the FN3K-Nrf2 pathway as a novel therapeutic target in cancer treatment.

The potential development of FN3K inhibitors represents a groundbreaking advancement in cancer therapy. Targeting FN3K could significantly reduce the aberrant activity of Nrf2, thereby curtailing its pro-tumorigenic effects. By inhibiting FN3K, we can sensitize cancer cells to oxidative damage and enhance their susceptibility to conventional treatments such as chemotherapy and radiotherapy. This strategy has the potential to effectively overcome the resistance mechanisms that often render current cancer therapies less effective.

Although research into FN3K inhibitors is still in its early stages, the preliminary findings are indeed promising. Current efforts are concentrated on identifying compounds that can selectively inhibit FN3K while sparing other crucial enzymatic pathways to avoid unintended consequences. Methods such as high-throughput screening, computational modeling, and structure-activity relationship studies are being employed to discover potent FN3K inhibitors. The successful development of these inhibitors could revolutionize cancer treatment by providing a targeted approach to diminish Nrf2-driven oncogenesis, offering new hope for patients facing aggressive and treatment-resistant forms of cancer.

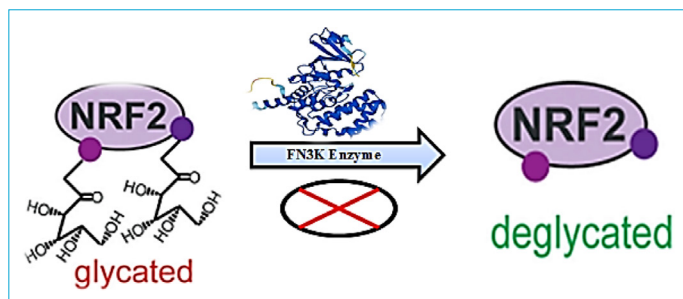


Figure 7. Schematic depiction is the mechanism of action of FN3K inhibitors. These inhibitors play a pivotal role in sustaining the Nrf2 transcription factor in its stabilized glycosylated state. This is achieved by preventing the FN3K enzyme, which is responsible for the deglycation process, from inducing destabilization.

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