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Mini-review

"NRF2 addiction" in lung cancer cells and its impact on cancer therapy

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ABSTRACT

Nuclear factor erythroid 2-like factor 2 (NRF2) is a master regulator of the antioxidant enzymes and the detoxification proteins that play major roles in redox homeostasis. Although it plays a protective role against tumorigenesis, emerging evidence has shown that the NRF2 pathway is frequently altered in different types of cancer, including lung cancer. NRF2 activation influences many of the hallmarks of cancer and their signaling pathways, mainly apoptosis, proliferation, angiogenesis, metastasis, and metabolic reprogramming to establish cellular metabolic processes leading to "NRF2 addiction" in lung cancer cells. Intriguingly, constitutive activation of NRF2 promotes cancer development as well as resistance to chemotherapy and radiotherapy, and these malignant phenotypes lead to a poor prognosis in lung cancer patients. Therefore, targeted inhibition of the NRF2 together with traditional chemotherapy, radiotherapy, and immunotherapy, may be a promising approach to improving the survival rates of the NRF2-addicted lung cancer cases. Here we summarize the recent advances in NRF2-addicted lung cancer.

1. Introduction

Lung cancer is one of the top causes of cancer deaths in the global population. Although the majority of lung cancers are caused by tobacco smoking, other factors can induce lung cancer such as family history/heritable factors [1], exposure to certain cooking fumes (particularly among Chinese women) [1], occupational and environmental exposures (radon and pollutants) [2], hormonal factors [3], pre-existing lung disease (including pneumonia and tuberculosis) [4], and exposure to ionizing radiation [4]. Small cell lung cancer and non-small cell lung cancer (NSCLC) account for 15% and 85% of all cases respectively [5]. NSCLC is further divided into 3 major pathologic subtypes: adenocarcinoma, squamous cell carcinoma, and large cell carcinoma [3].

The Kelch-like ECH-associated protein 1 (KEAP1)/nuclear factor erythroid 2-like factor 2 (NRF2)/Cullin3 (CUL3) system is a pivotal defense mechanism against oxidative and electrophilic stress where NRF2 transactivates the expression of various cytoprotective genes [6]. Due to the cytoprotective activity of NRF2, several natural and synthetic compounds which function as NRF2 activators have been identified and developed for therapeutic use. For instance, natural and synthetic products that activate NRF2 such as sulforaphane [7], dimethyl fumarate [8], and resveratrol defend cells against carcinogens and are involved in cytoprotection [9]. Although NRF2 activation in response to stress is beneficial to health, persistent NRF2 activation in cancer cells has deleterious effects on cancer-bearing hosts by conferring therapeutic resistance and aggressive tumorigenic activity on cancer cells [10]. Cancer cells with persistent activation of NRF2 often develop "NRF2 addiction" and show malignant phenotypes leading to poor prognoses in cancer patients [11].

In this review, we summarize recent studies that have revealed the genetic features of NRF2-addicted lung cancer cells, canonical and non-canonical regulation of NRF2, the role of NRF2 in cancer cell metabolism, and therapeutic strategies for NRF2 addiction.

2. Molecular aberrations in non-small cell lung cancer

According to data from The Cancer Genome Atlas (TCGA), most of tumors have frequent alterations in ten canonical pathways: cell cycle, Hippo, Myc, Notch, NRF2, phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt), receptor tyrosine kinase (RTK)-RAS, TGFβ signaling, tumor protein p53 (p53) and ß-catenin/Wnt that control cell-cycle progression, apoptosis, and cell growth. So, genetic changes in these signaling pathways provide evidence of common dysfunctions in cell cycle control, response to oxidative stress, apoptotic signaling, and/or cell differentiation that are considered to be the most common hallmarks of different types of cancer [12]. However, the NRF2 pathway

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Abbreviations

NRF2	nuclear factor erythroid 2-like factor 2
NSCLC	non-small cell lung cancer
KEAP1	Kelch-like ECH-associated protein 1
CUL3	cullin3
TCGA	The Cancer Genome Atlas
PI3K	phosphoinositide 3-kinase
Akt	protein kinase B (PKB), a serine/threonine kinase
RTK	receptor tyrosine kinase
p53 (TP53)	tumor protein p53
LUSC	lung squamous cancer
Neh	NRF2-ECH homology-like domain
sMAF	small musculoaponeurotic fibrosarcoma
ARE	antioxidant response element
PKC	protein kinase C
GSK-3β	glycogen synthase kinase-3 beta
MAPK	mitogen-activated protein kinase
ERK	extracellular regulated protein kinase
SCF complex	Skp, cullin, F-box containing complex, a multi-protein E3 ubiquitin ligase complex
Mkp-1	MAP kinase phosphatase 1
Hrd1	Hmg CoA reductase degradation 1
CDK20	cyclin-dependent kinase 20
p62	nucleoporin p62
ROS	reactive oxygen species
miRNA (miR)	microRNA
PPP	pentose phosphate pathway
G6PD	glucose-6-phosphate dehydrogenase
PGD	phosphogluconate dehydrogenase
Tkt	transketolase
NADPH	nicotinamide adenine dinucleotide phosphate
PTEN	phosphatase and tensin homolog
PHGDH	phosphoglycerate dehydrogenase
PSAT1	phosphoserine aminotransferase
SHMT2	mitochondrial serine hydroxymethyl transferase
SLC7A11	solute carrier family 7 member 11
ATRA	all-trans-retinoic acid
RXRα	retinoid X receptor alpha
RARα	retinoic acid receptor alpha
PD-L1	programmed death-ligand 1
GSH	reduced glutathione
IL-11	interleukin 11
AKR1C1	aldo-keto reductase family 1 member C1
ABCC2	ATP binding cassette subfamily C member 2
TXNRD1	thioredoxin reductase1
MEK	MAPK/ERK kinase
TSC	tuberous sclerosis complex
MTOR	mammalian target of rapamycin
PLC	phospholipase C
NF κB	nuclear factor kappa-light-chain-enhancer of activated B cells
GAB	GRB2-associated-binding protein
JAK	Janus kinase
STAT	signal transducer and activator of transcription
ATM	ataxia telangiectasia mutated
MDM2	mouse double minute 2 homolog
CDKN	cyclin dependent kinase inhibitor
CDKs	cyclin dependent kinases
RB1	retinoblastoma tumor suppressor gene
E2F	E2 promoter binding factor

has the lowest overall frequency of alteration; it is changed most frequently in lung cancer and esophagogastric squamous cell carcinoma [12].

In addition, multiple oncogenic and tumor suppressor pathways are involved in the initiation and progression of lung cancer [13], including retrovirus-associated DNA sequences (RAS), epidermal growth factor receptor (EGFR) mutations, and echinoderm microtubule-associated protein-like anaplastic lymphoma kinase (EML4-ALK) fusion; in addition, changes in novel signaling pathways including Notch [14], P53, cell cycle, and the KEAP1/NRF2 axis [12] are involved in lung cancer

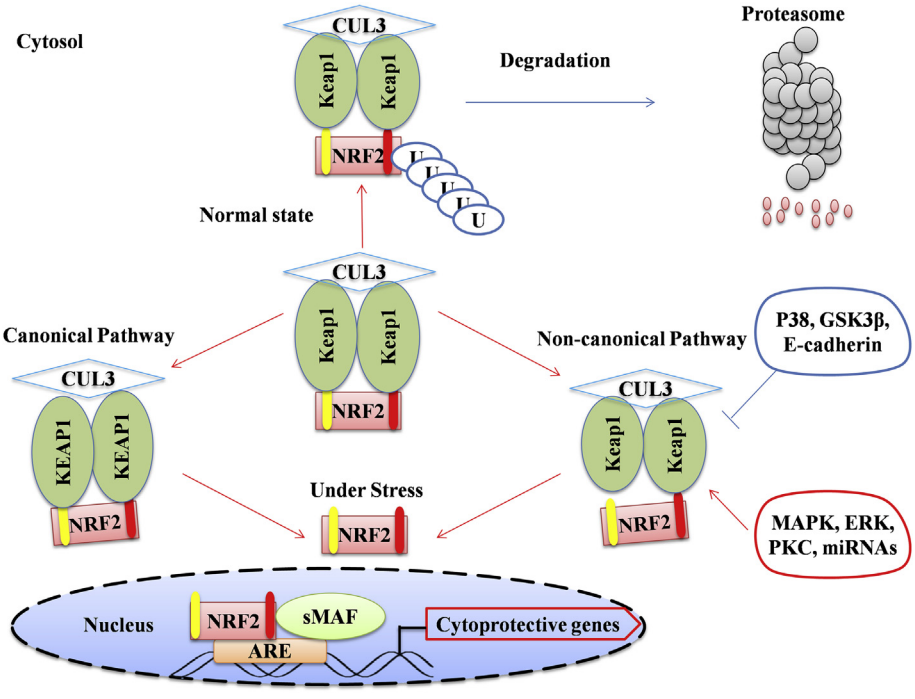

Fig. 1. KEAP1-dependent and KEAP1-independent regulation of NRF2. Under homeostatic conditions (normal state), the KEAP1 homo-dimer binds to NRF2 with ETGE and DLG motifs which leads to the CUL3-mediated ubiquitination and proteasomal degradation. Under oxidative stress, the modification of cysteine residues on KEAP1 results in diminished NRF2 ubiquitination. NRF2 protein levels are thus increased and NRF2 is translocated into the nucleus where it associates with sMAF subsequently binding the ARE sequences on target genes, and regulating their transcription. In Keap1-independent regulation, NRF2 is activated by several alternative mechanisms (MAPK, ERK, PKC and miRNAs) and inhibited by other alternative mechanisms (P38, GSK-3β and *E*-cadherin).

tumorigenesis. According to the National Comprehensive Cancer Network guidelines, genomic testing paradigms for *EGFR*, *ALK*, *ROS1*, *BRAF*, and *PD-L1* in addition to *EGFR* insertion 20 mutations, *RET* rearrangements, and *MET* exon 14 mutations are still being actively investigated in clinical studies and hold potential for clinical treatment [15].

Specifically, genetic alterations of the NRF2 pathway have been reported predominantly in TCGA lung squamous cancer (LUSC) than in lung adenocarcinoma [16,17]. Altogether, changes in the KEAP1/NRF2/CUL3 pathway have been reported in a third of all TCGA LUSC cases [18]. Besides TCGA data, ~40% of KEAP1/NRF2/CUL3 pathway changes have been reported in LUSC patients from East Asia [19].

3. Regulation of NRF2

NRF2 belongs to a transcription factor family which is characterized by a unique Cap'n'Collar motif followed by a well-conserved basic region-leucine zipper structure and consists of seven ECH homology-like domains, namely Neh1–7 [20,21]. The expression and activity of NRF2 are tightly controlled by several canonical and non-canonical pathways (Fig. 1).

3.1. Canonical pathway

KEAP1, a cysteine-rich and redox-sensitive protein, contains five functional domains the N-terminal region, the broad complex, tram track, and bric-a-brac domain, an intervening linker domain, the double glycine/Kelch repeats, and the C-terminal region [22]. Under normal conditions, the Kelch domains of the KEAP1 homodimer bind to the two motifs (DLG with low affinity and ETGE with high affinity) present in the Neh2 domain of NRF2 and targets NRF2 for ubiquitination followed by proteasomal degradation [23]. Under stress conditions, highly-reactive cysteine residues in KEAP1 are oxidized, which prevents KEAP1 from binding to NRF2 for ubiquitination [24]. Consequently, NRF2 accumulates and is translocated into the nucleus where it heterodimerizes with small musculoaponeurotic fibrosarcoma (sMAF) protein *via* its Neh1 domain. The NRF2-sMAF heterodimer binds to the antioxidant response element (ARE) and induces transactivation of its target genes [25] (Fig. 1).

3.2. Non-canonical pathways

Besides the KEAP1-dependent regulation of NRF2, alternative mechanisms related to NRF2 activation have been reported, such as phosphorylation [26,27], deacetylation [28], and cysteine modification [29]. Non-canonical pathways involved in the regulation of NRF2 include protein kinase C (PKC) [26], glycogen synthase kinase-3 beta (GSK-3β) [27], mitogen-activated protein kinase (MAPK) cascades [30], the PI3K/AKT pathway [31], and extracellular regulated protein kinases (ERK) [32] (Fig. 1).

Interestingly, sirtuin 2 maintains cellular iron homeostasis by binding and deacetylating NRF2 on lysines 506 and 508, which leads to a reduction of total nuclear NRF2 levels [33]. Recently, we identified cross-talk between MAP kinase phosphatase 1(Mkp-1) and the NRF2 pathway in liver injury and intestinal inflammation in mouse models [34,35]. Our studies showed that direct interaction of the DIDLID motif of NRF2 with Mkp-1 leads to increased NRF2 stability and positive regulation of the NRF2 pathway. Moreover, we identified Mkp-1 as a target gene of NRF2, as Mkp-1 possesses functional ARE sites in its promoter region.

Intriguingly, Hmg CoA reductase degradation 1 (Hrd1), also known as Synoviolin, is a novel E3 ubiquitin ligase that regulates NRF2 through an interaction between the C-terminal domain of Hrd1 and the Neh4-5 domains of NRF2 [36]. Hrd1 mediates NRF2 degradation in a liver cirrhosis model [36]. In certain cases, the non-canonical regulation of NRF2 may act in concert with or even independent of the canonical KEAP1 pathway, playing a crucial role in pathogenesis [37]. Thus, focusing on the multiple regulatory mechanisms of NRF2 has important implications for understanding the pathology and designing new therapeutic strategies for NRF2-mediated diseases.

4. Mechanisms conferring “NRF2 addiction”

NRF2 activation confers enhanced progression, resistance to therapy, and increased antioxidant capacity, leading to the development of “NRF2 addiction” in lung cancer cells. The concept of “NRF2 addiction” emphasizes the apparent dependence of lung cancer cells on NRF2 pathway genes for maintenance of the malignant phenotype. This persistent activation can be regulated at different molecular levels including genomic alteration, changes in the levels of transcription and translation, and post-translation modification [38].

4.1. Genetic and epigenetic changes in KEAP1/NRF2 genes

Besides the recurrent loss of exon 2 of NRF2, mutations in the KEAP1 and NRF2 genes are the main causes of constitutive NRF2 activation [39,40]. The promoter region of KEAP1 is hypermethylated in lung cancer cells, leading to a reduction of KEAP1 expression and the accumulation of NRF2 [41,42]. A very recent study by Kerins and Ooi reported a catalog of NRF2 gain-of-function mutations in TCGA, revealing 226 NRF2-mutant cases among 10,364 patients with different cancers [43]. Interestingly, somatic KEAP1 mutations are most frequently reported in lung adenocarcinoma [17] and NRF2 mutations in LUSC [43]. KEAP1 mutations do not significantly alter the mRNA expression of NRF2 and KEAP1 but they increase the expression of target genes downstream of NRF2, suggesting that KEAP1 and NRF2 interact primarily at the protein level and that KEAP1 mutations strongly affect NRF2 signaling and the cellular response to platinum chemotherapy in NSCLC [44]. Thus, KEAP1 might be used as a specific biomarker for predicting the response to chemotherapy [44].

4.2. Transcriptional regulation

The transcriptional levels of the NRF2 gene influence the protein levels of NRF2 [45]. Several oncogenes may increase the transcriptional levels of NRF2 and NRF2-regulated genes including C-MYC, K-RAS, and BRAF, resulting in a marked elevation of cytoprotection of cancer cells [18,31,46]. Briefly, it has been shown that the oncogenes K-RAS and B-RAF transcriptionally increase the NRF2 expression and reduce the intracellular production of reactive oxygen species (ROS), which ultimately leads to the hyperactivation of NRF2. Likewise, oncogenic K-RAS binds to exon 1 of NRF2 by the TPA response element and upregulates NRF2 gene expression that confers chemoresistance on NSCLC cells [47].

4.3. Translational regulation

MicroRNAs (miRNAs) are small noncoding molecules that bind to the 3′-untranslated regions of genes and regulate their mRNA degradation or the inhibition of translation. Singh et al. demonstrated that activated NRF2 upregulates the expression of pentose phosphate pathway (PPP) genes by inhibiting the expression of the miR-1 and miR-206 miRNAs in NSCLC cells [48]. Another interesting study revealed that miR-155 represses the NRF2 expression in arsenic-transformed bronchial epithelial cells and promotes the malignant transformation of lung cells [49].

4.4. Post-translational modification

The Neh2 domain of NRF2 contains serine 40 that is phosphorylated by PKC. Phosphorylation results in KEAP1-NRF2 dissociation and the nuclear localization of NRF2 [38]. Moreover, casein kinase 2

phosphorylates the transcription activation domain of NRF2, and this leads to the nuclear translocation and activation of NRF2 target genes in neuroblastoma cells [26]. GSK-3β phosphorylates the serine residues present in the Neh6 domain of NRF2 and promotes SCF/β-TrCP-dependent degradation [27]. AMP-activated protein kinase phosphorylates NRF2 at the Ser 550 residue, and acts as an interrupter of GSK-3β-NRF2 binding, which is followed by the nuclear translocation of NRF2 and ARE-driven gene expression [50].

Post-translational changes of NRF2, including phosphorylation, ubiquitination, or acetylation, alter NRF2 protein levels and subcellular localization; consequently, these events need to be carefully examined in lung cancer cells to determine their functional impact on NRF2 transcriptional activity.

4.5. Activation of NRF2 by PI3K/AKT

The classical oncogenic PI3K pathway is considered to be a nutrient-sensing pathway in which the action of insulin by increasing glucose activates PI3K which catalyzes the phosphorylation of lipid phosphatidylinositol 4,5-bisphosphate to produce phosphatidyl inositol 3,4,5-triphosphate, a reaction that is reversed by tumor suppressor phosphatase and tensin homolog (PTEN). The generation of phosphatidyl inositol 3,4,5-triphosphate is an important step in the activation of AKT that mediates the inhibition of GSK-3β, which acts as a negative regulator of NRF2 by its phosphorylation to promote the binding of beta transducing repeat containing protein followed by degradation by Cullin1 (Cul1) [27,51,52]. An activated PI3K signal increases NRF2 accumulation in the nucleus, thereby enhancing multiple biological processes [18,31,46].

4.6. KEAP1-NRF2 binding interrupters

Cyclin-dependent kinase 20 (CDK20) is a novel KEAP1-interacting protein, which competes with NRF2 for KEAP1 binding through its N-terminal ETGE motif [53]. Intriguingly, CDK20 is overexpressed in lung cancer tissue and is critical for promoting cell proliferation and radio- and chemoresistance in lung cancer [53]. In addition, the autophagy-related protein p62, a scaffold protein that brings cargo into the autophagosome, acts as a substrate of autophagic degradation [54], and acts as interrupter of KEAP1-NRF2 binding by directly binding to KEAP1 [55], since it contains an STGE motif that, upon phosphorylation of the serine residue, mimics the high-affinity ETGE motif and thus competes with NRF2 for KEAP1 binding [56]. Consequently, p62 sequesters KEAP1 into the autophagosome and liberates NRF2 from KEAP1-mediated degradation and promotes the activation of NRF2 [54].

5. Functions mediated by NRF2 in cancer progression and maintenance

Elevated NRF2 protein levels have been found in multiple human cancers and are associated with tumor promotion and progression through the transcriptional activation of a wide range of metabolic genes and cytoprotective genes that protect cancer cells and promote their proliferation and metastasis [31,57–60].

5.1. Oxidative stress regulation

Many genes regulated by NRF2 are key enzymes involved in the detoxification and antioxidant responses of cancer cells such as heme oxygenase 1, NAD(P)H dehydrogenase quinone 1 (NQO1), glutathione S-transferase, superoxide dismutase, catalase, aldehyde dehydrogenase, glutamate cysteine ligase, and phase II enzymes [61]. Cancer cells with constitutive activation of these enzymes are selected as a means of enabling adaptation to a hostile microenvironment, chemotherapy, radiotherapy, or high endogenous ROS levels [60].

5.2. Metabolic reprogramming

NRF2 has emerged as a key regulator of metabolic reprogramming in which dividing cancer cells take up more glucose and metabolize it through aerobic glycolysis (Warburg effect) [62]. This metabolic alteration, a hallmark of cancer cells, provides more anabolic precursors and reducing equivalents which are indispensable for their rapid growth and proliferation [62]. Upon control of the expression of glucose-6-phosphate dehydrogenase (G6PD), phosphogluconate dehydrogenase (PGD), transketolase, and transaldolase 1, NRF2 redirects glucose to the PPP, producing nicotinamide adenine dinucleotide phosphate (NADPH) as reducing equivalents and ribose 5-phosphate as the key substrate for nucleotide synthesis [62]. Inactivation of KEAP1 and PTEN in the mouse lung promotes adenocarcinoma formation, and the tumorigenesis is associated with reprogramming of the PPP [63]. In addition to the PPP pathway, NRF2 can directly promote *de novo* nucleotide synthesis by regulating the transcription of methylene tetrahydrofolate dehydrogenase 2 and phosphoribosyl pyrophosphate aminotransferase [51]. In lung cancer, activation of NRF2 can influence the PPP and tricarboxylic acid cycle *via* reducing miR-1 and miR-206 expression, resulting in the elevation of metabolic gene expression (G6PD, PGD, and TKT) associated with reduced survival in patients with lung cancer [48].

5.3. Glutamine metabolism

Some cancer cells also display an addiction to glutamine metabolism which alleviates oxidative stress by supporting NADPH production [64]; therefore, glutaminase, the enzyme that converts glutamine to glutamate, has emerged as a potential therapeutic target [65]. Briefly, NRF2 promotes the transport of glutamine by enhancing the expression of the glutamine transporter and alanine-serine-cysteine transporter 2 [66]. NRF2 regulates the expression of glutaminase, which converts glutamine to glutamate in mitochondria. Glutamate is further metabolized by glutamate dehydrogenase or aminotransferases to α-ketoglutarate, replenishing the TCA cycle [67]. Recently, studies have shown that inhibitors of glutaminase such as CB-839 may be considered as an alternative approach to the suppression of NRF2 [65,66,68]; for instance, LKB1-deficient cells with persistent activation of the KEAP1/NRF2 pathway display enhanced survival and this pathway plays a crucial role in the maintenance of energetic and redox homeostasis in a glutamine-dependent manner [65].

5.4. Serine/glycine biosynthesis

NRF2 promotes serine/glycine biosynthesis by enhancing the transcription of key genes in this process, including PHGDH encoding phosphoglycerate dehydrogenase, PSAT1 encoding phosphoserine aminotransferase, and SHMT2 encoding mitochondrial serine hydroxymethyl transferase [69]. Enhanced serine/glycine biosynthesis provides substances for glutathione synthesis and produces a one-carbon unit for nucleotide production, which promotes tumorigenesis.

5.5. Cell proliferation and differentiation

A large body of evidence has suggested that the KEAP1/NRF2 axis is involved in cell proliferation and differentiation by regulating the cellular levels of ROS; the proliferation and differentiation of most cell types are often modulated by the cellular redox balance [70,71]. In addition, analyses of the genome-wide distribution of NRF2 have revealed new NRF2 target genes whose products are involved in cell proliferation and differentiation. Studies have shown that NRF2 supports cell differentiation by preventing oxidative stress, as demonstrated by the elevation of lipid peroxidation and decrease of glutathione and antioxidant enzyme activity in Nrf2-deficient mice compared to wild-type mice. Furthermore, NRF2 activation inhibits

Table 1
NRF2 and it downstream effectors/inhibitors.

Type of inhibition	Source	Compound	Mechanism	Ref.
A: NRF2 inhibitors	*Brucea javanica* plant	Brusatol	↓ NRF2 protein level	[99]
	Alkaloid febrifugine plant	Febrifugine, Halofuginone	↓ NRF2 protein accumulation	[116]
	Synthetic inhibitors	AEM1	↓ NRF2-driven genes	[95]
		ML385	Blocked NRF2 nuclear translocation and transcriptional activity	[96]
		Clobetasol propionate	↑ oxidative stress, ↓NRF2 nuclear accumulation and ↑NRF2 degradation through the β-TrCP-dependent pathway	[117]
	Flavonoid	Luteolin	↑NRF2 mRNA degradation	[97]
		4-Methoxychalcone	↓phosphorylated Akt	[118]
		3′,4′,5′,5,7-Pentamethoxy flavone	↑KEAP1 expression and ↓ phosphorylated ERK	[119]
		Apigenin	↓phosphorylated Akt	[120]
		Chrysin	↓phosphorylated Akt and ↓phosphorylated ERK	[121]
	Vitamin derivatives	Ascorbic acid	↓Nuclear accumulation of Nrf2	[122]
		Retinoic acid	↓DNA binding and ↓ Nrf2 nuclear import	[123]
	Chinese herb *Salvia miltiorrhiza*	Cryptotanshinone	↓NRF2 and its target genes	[124]
	Fungal mycotoxin	Ochratoxin A	↓NRF2 nuclear translocation, ↓NRF2 mRNA	[125]
	Cinnamomi cortex extract	procyanidins	↓NRF2 expression, ↑proteasome-independent degradation of nuclear NRF2	
	Coffee constituent	Trigonelline	↓Nuclear accumulation of Nrf2	[126]
	Type 2 diabetes drug	Metformin	↑microRNA 34a that inhibits NRF2	[127]
	Anti-tubercular drug	Isoniazid	↓Nuclear accumulation of NRF2	[128]
	Novel nano emulsion of lipid alcohols	Metadichol	↓NRF2 activation	[129]
	Synthetic compound	K67 (*N*-[2-acetonyl-4-(4-ethoxybenzenesulfonylamino) naphthalene-1-yl]-4-ethoxybenzenesulfonamide)	↓phosphorylated p62–KEAP1 interaction that decreases NRF2 level	[130]
	RXRα-specific ligand	Bexarotene	↓Transcriptional activity of NRF2	[131]
	Natural product	Camptothecin	↓NRF2 expression	[125]
		Oridonin	↓NRF2nuclear translocation	[132]
B: Inhibitors of NRF2 target genes				
Serine synthesis inhibition	Synthetic inhibitors	CBR-5884	Inhibition and disruption PHGDH	[107]
PPP inhibition	Androgen precursor	DHEA	Inhibitor of G6PD	[108]
	Glucoside of Resveratrol	Polydatin	Inhibitor of G6PD	[108]
GSH synthesis inhibition	Sulfoximine	BSO	Inhibitor of γ-glutamyl-cysteine synthetase	[110]
Aldo-keto reductase family 1 member C1 (AKR1C1) inhibitor	Synthetic compound	Aspirin	↓ AKR1C1 gene	[133]
ATP Binding Cassette Subfamily C Member 2 (ABCC2) inhibitor	Synthetic compound	Sulfinpyrazone	↓ ABCC2 gene	[134]
Thioredoxin reductase1 (TXNRD1) inhibitor	Synthetic compound	Arsenic Trioxide	↓ TXNRD1gene	[135]
PGD gene inhibitor	Synthetic compound	Gadopentetate dimeglumine	↓ PGD gene	[136]
Heme oxygenase-1 (HO-1) inhibitor	Synthetic heme analog	Tinprotoporphyrin IX	Blockade of HO-1 function	[137]
Novel Keap1/Nrf2 pathway inhibitor	Natural compound isolated from *Streptomyces* sp	K-563	↓Expression of Keap1/Nrf2 pathway downstream target genes	[138]

osteoclast differentiation by reducing the intracellular ROS [71,72]. In lung cancer cells, NRF2 induces proliferation independently of growth factor signaling, because tyrosine kinase inhibitors are unable to inhibit the proliferation of cancer cells with constitutive NRF2 activation [73] and cancer cells with mutant PTEN and PI3K-AKT, resulting in higher proliferation rates and increased tumorigenicity as noted above [74].

5.6. Ferroptosis

Ferroptosis is a nonapoptotic, iron-dependent form of cell death that can be activated in cancer cells by natural stimuli and synthetic agents. NRF2 in gliomas diminishes ferroptotic cell death through upregulation of the SLC7A11 gene (Solute Carrier Family 7 Member 11) and amplification of glutamate secretion thereby impacting the tumor microenvironment and cancer cell growth [75]. On the other hand, increasing ferroptosis may improve NSCLC therapy; it has recently been shown that radioresistance decreases as ferroptosis increases in NSCLC cells [76]. Therefore, using inhibitors of NRF2 activation may be useful in improving the traditional therapy for NSCLC.

5.7. Angiogenesis

The hypoxic microenvironment of tumors affects their growth and progression by enhancing tumor angiogenesis by activating the transcription factor HIF-1α that is considered to be the major transcriptional regulator of hypoxia-induced angiogenesis through the transactivation of genes encoding multiple angiogenic growth factors including vascular endothelial growth factor (VEGF), basic fibroblast growth factor, cytokines, and extracellular matrix remodelers to generate vasculature [22]. At the molecular level, NRF2 blockade suppresses cancer angiogenesis by inhibiting the hypoxia-induced activation of HIF-1α-VEGF signaling [77]. This could be due to the NRF2 target gene NQO1 that encodes a protein that prevents HIF-1α degradation [78].

5.8. Metastasis

Metastasis is among the hallmarks of cancer [79] and the most common contributor to mortality in lung cancer patients [80]. It is a multi-step phenomenon through which a tumor spreads from its primary site and forms secondary growths at a distance [81]. Activated NRF2 induced by increasing heme oxygenase-1 expression, which reduces the levels of free heme and inhibits the degradation of Bach1, which in turn leads to an increased Bach1 level has been found in lung cancer cases with metastasis. Stabilized Bach1 promotes the activation of pro-metastatic genes such as CXCR4 and matrix metallopeptidases. Therefore, drugs targeting this metastatic pathway might be a novel therapeutic avenue for lung cancer patients with alterations in the Keap1-Nrf2 pathway [59,60].

5.9. Epithelial-mesenchymal transition (EMT)

The EMT is a process during which epithelial cells lose their polarity and cell-cell adhesion, and then gain a mesenchymal phenotype with migratory and invasive properties. The EMT is considered to be a vital mechanism by which epithelial cancer cells acquire a malignant phenotype, especially invasion and metastasis [82]. During the EMT, epithelial cells lose expression of the adhesion protein *E*-cadherin, a well-known tumor suppressor, and the loss of its expression in tumor cells results in tumor progression and metastasis [22,82]. Moreover, NRF2 promotes the EMT by down-regulation of *E*-cadherin expression in different types of cancers showing worse outcomes [83].

5.10. Tumor immune microenvironment

The interaction between a tumor cell and its microenvironment is an important determinant of the pathological nature of cancers, particularly their tumorigenicity [84]. Interleukin-6 (IL-6), one of the common cytokines in the tumor microenvironment, is overexpressed in almost all types of tumor [85]. It induces tumorigenesis by regulating many of the hallmarks of cancer and multiple signaling pathways, including apoptosis, proliferation, angiogenesis, and metastasis. Moreover, IL-6 protects cancer cells from therapy-induced DNA damage, oxidative stress, and apoptosis by facilitating the repair and induction of antioxidant and anti-apoptotic pathways [85]. Recently, studies have shown that the role of NRF2 in regulating the immune microenvironment of tumors by promoting the expression of cytokines such as IL-6 and IL-11 results in immune escape and acceleration of tumor progression [84,86]. Indeed, aberrant NRF2 pathway activity alters the immune microenvironment of lung cancer as shown by the reduced leukocyte infiltration associated with lung cancer mutations in KEAP1 [87]. Therefore, blocking IL-6 and/or IL-11 could be a potential therapeutic strategy for NRF2-addicted cancers.

Moreover, extracellular vesicles (EVs), small membranous structures released by various cell types as alternative pathways, maintain cellular homeostasis by removing toxic oxidized molecules. EVs are divided into three major types: exosomes, microvesicles, and apoptotic bodies. Accumulating evidences has shown the prominent role of EVs in mediating intercellular communication in the presence of local and systemic inflammation that result from such oxidative stresses as cancer [88,89]. EVs can deliver bioactive molecular contents such as proteins, DNA, mRNAs, miRNA and other nuclear materials. In addition, EVs are involved in therapeutic resistance and tumor progression. Indeed, following chemotherapy, mesenchymal stem cell (MSC)-derived EVs play a protective role in cancer cells through activation of NRF2/ARE, reducing chemotherapy induced apoptosis [88,90–92]. The role of NRF2 in EVs-mediated therapeutic resistance and tumor progression is unknown, however, EVs protect against acute kidney injury through promoting NRF2 pathways [90].

6. Therapeutic strategies for NRF2 addiction

There is an increasing demand for the development of new therapeutic strategies for NRF2-addicted lung cancer based on targeting NRF2 and its upstream regulators and downstream effectors along with conventional therapies (chemotherapy, radiotherapy, and immunotherapy) [11]. More accessible approaches for these are NRF2 inhibitors [37], gene therapy [37] and immunotherapy based on NRF2 [63], and inhibitors of its downstream effectors.

6.1. NRF2 inhibitors

Several NRF2 inhibitors have been studied for lung cancer therapy (Table 1) but currently none has yielded strong and indisputable results. Most of the NRF2 inhibitors identified are extracted from plants [37]; their specificity, bioactivity, and toxicity are major obstacles to overcome in developing clinical therapies. Some of these inhibitors include flavonoids [93], alkaloids [94], and novel synthetic compounds, such as ARE expression modulator 1 and ML385 [95,96]. Moreover, some vitamins and commercial drugs have been developed as NRF2 inhibitors, such as ascorbic acid, all-trans-retinoic acid (ATRA), anti-tubercular agents, metformin, and glucocorticoids. We identified luteolin as a strong inhibitor of Nrf2 in NSCLC cells [93] and *in vivo* [97]. Surprisingly, a recent interesting clinical study by Huppke and colleagues using luteolin along with ascorbic acid to treat a patient with NRF2 mutations (multisystem disorder) successfully modulated the dysregulation of NRF2 [98]. However, more clinical studies are warranted to determine the specificity of luteolin inhibition. Brusatol has an NRF2 inhibitory effect in A549 human lung adenocarcinoma cells both *in vitro* and *in vivo* [99]. However, further studies showed that Brusatol is not a specific NRF2 inhibitor and it decreases the expression of a great number of proteins, especially those with a short half-life [100].

Several nuclear receptors, including retinoid X receptor alpha (RXRα) [101], retinoic acid receptor alpha (RARα) [102], retinoic acid receptor gamma [103], estrogen receptor alpha [104], nuclear receptor peroxisome proliferator-activated receptor gamma [20], estrogen-related receptor beta [105], and glucocorticoid receptor have also been shown to inhibit the NRF2-ARE pathway [20,102]. For instance, we found that RXRα physically interacts with NRF2 in the Neh7 domain, and negatively regulate ARE driven gene expression [20,101]. Moreover, ATRA, the ligand for RARα, has also been proposed to be an NRF2 inhibitor [102]. In the presence of ATRA, NRF2 forms a complex with RARα, and can no longer bind to ARE sequences, blocking activation of the pathway [102].

6.2. Immunotherapy-based NRF2 inhibition

With regard to targeting the downstream effectors of NRF2, programmed death-ligand1 (PD-L1) is directly controlled by NRF2 through its ability to bind to the regulatory region of the PD-L1 gene [106]. In addition, the tumor microenvironment of NRF2-addicted lung cancer cells has high levels of immunosuppressive proteins such as PD-L1, as confirmed by KEAP1/PTEN Flanking/flanked by LoxP ($KEAP1^{f/f}$/$Pten^{f/f}$) tumor-bearing lungs [63]. Moreover, checkpoint inhibition by anti-PD-1 results in tumor regression with a concomitant increase in the numbers of infiltrating lymphoid cells and decreasing PD-L1 expression in tumor cells, showing that immunotherapy responses can be obtained when the tumor cell expression of PD-L1 is high [63]. Interestingly, NRF2-addicted lung cancer cells show high expression of NRF2 that might increase the expression of PD-L1 [106], so this type of tumor may be vulnerable to immunotherapy, bypassing the chemo- and radio-resistance mechanisms [63]. Intriguingly, activation of the NRF2 pathway could provide additional immunomodulation that sensitizes lung adenocarcinoma to immunotherapy and improves its efficacy [87].

6.3. Inhibitors of downstream effectors

There are many downstream effectors of NRF2 and inhibition of these effectors in combination with conventional cancer therapy may improve prognosis and survival rates (Table 1).

Serine biosynthesis inhibition: CBR-5884 compound inhibits *de novo* serine synthesis in cancer cells by inhibiting and disrupting the oligomerization state of the enzyme PHGDH, which catalyzes the first step of serine biosynthesis [107].

PPP inhibition: dehydroepiandrosterone, an androgen precursor, is an inhibitor of G6PD, the rate-limiting enzyme in the PPP [108]. It is rapidly converted into steroid hormones *in vivo* and its efficacy as an inhibitor of G6PD is under dispute [108]. Polydatin, a glucoside of resveratrol, is an inhibitor of G6PD that causes impairment of NADPH production, increases ROS-mediated endoplasmic reticulum stress, increases apoptosis, and inhibits invasion [108].

Glutathione synthesis inhibition: buthionine sulfoximine, or BSO, a potent inhibitor of glutathione (GSH) synthesis, inhibits γ-glutamylcysteine synthetase which is the rate-limiting step of GSH biosynthesis, enhances the cytotoxic effects of various drugs in cancer cells, and induces the depletion of tumor GSH [109,110]. Moreover, targeting downstream GSH and other metabolic pathways is viable in NRF2-addicted lung cancer cells, and this highlights the dependence of these cancers on NRF2-driven metabolic pathways [87].

IL11 antagonist: tumor microenvironment studies have shown that NRF2 in NRF2-addicted cancer cells induces expression of the *IL11*gene which mediates the malignant phenotypes. So, targeting IL11 may be a future therapeutic approach for inhibiting tumorigenesis and resistance to conventional cancer therapy [84].

7. Future perspectives

In view of the high frequency of tumors displaying NRF2 hyperactivation in lung cancer, NRF2 is considered to be a potential pharmacological target. Unfortunately, no known NRF2 inhibitor has entered clinical trials, despite evidence for the effectiveness of NRF2 inhibition in enhancing the efficacy of chemotherapy and in reducing tumor progression. Thus, there is an urgent need for improved NRF2 inhibitors. A better understanding of the mechanisms underlying NRF2 regulatory mechanisms may provide an alternative to directly inhibiting Nrf2.

Discovery of the unique metabolic features of transformed cells has spurred much interest in exploiting their metabolic vulnerabilities for drug discovery [109,110]. While cancer cells share common hallmarks, tumorigenic drivers uniquely influence the direction and extent of metabolic reprogramming. The new paradigm of incorporating combinatorial CRISPR screening, transcriptomic information, and metabolic flux measurements presented by Zhao et al. [111] will provide a new platform to address this limitation. Indeed, recent work has implicated *KEAP1* mutational status as a driver of metabolic reprograming and potential targeting of glutaminase in preclinical models of lung adenocarcinoma [112]. As such, mutation of *KEAP1* increases intracellular glutathione levels and the need for cysteine, causing an increased need for glutamine anaplerosis to support glutamate/cysteine antiporter flux (*SLC7A11*) [113].

By interrogating metabolism at the network-level, new therapeutic targets may be identified in lung cancer with NRF2 hyperactivation, and clinicians may become better equipped to identify the most responsive patients.

Research into genetic signatures has focused on the early diagnosis of curable lung cancers. With the greater availability of sequencing or RNA-seq analysis, tumor mutations and transcriptional profiles are being studied and are providing valuable information. Gene signatures can potentially be used as diagnostic or prognostic markers to guide clinical decisions. Our recent studies identified a specific gene-expression signature regulated by the NRF2 pathway in lung adenocarcinoma [114] and head-neck squamous cell cancers [114]. Similarly, the $NRF2^{ACT}$ gene-expression signature that includes 28 genes might also serve as a biomarker of benefit from adjuvant cisplatin-based chemotherapy in lung cancer [115]. Based on the unique metabolic activity of NRF2-addicted cancers, detailed metabolite analysis might lead to the identification of downstream genes of NRF2 that can be used as diagnostic and prognostic biomarkers. Indeed, as diagnostic techniques advance and understanding of biology accumulates, targeting Nrf2 under more circumstances in cancer will become more practical.

CRediT authorship contribution statement

Ahmed Hammad: Conceptualization, Writing - original draft, Writing - review & editing. **Akhileshwar Namani:** Writing - review & editing. **Mohamed Elshaer:** Writing - review & editing. **Xiu Jun Wang:** Conceptualization, Writing - review & editing, Project administration, Funding acquisition. **Xiuwen Tang:** Conceptualization, Writing - review & editing, Supervision, Project administration, Funding acquisition.

Declaration of competing interest

Authors declare that they have no competing interests.

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