Review

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Review

NRF1 or NRF2: Emerging Role of Redox Homeostasis on PERK/NRF/Autophagy Mediated Antioxidant in Tumor and Patient Dependent Chemo Sensitivity

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Abstract: Chemo-resistance is a substantial challenge in the realm of cancer treatment that requires exploring new therapeutic approaches for effective mitigation. Achieving this goal requires examination of the molecular mechanisms involved in both tumor growth and therapeutic interventions. The potential of NRF2 (Nuclear factor E2-related factor 2) in addressing resistance to chemotherapy across diverse cancer types highlights its value as a promising therapeutic approach based on cancer characteristics. Manipulating the NRF2 signaling pathway has a dual impact, offering promise for both preventing and treating cancer, as well as inhibiting carcinogenesis. The influence of the NRF2/KEAP1 pathway on the progression of tumor formation and resistance to drugs has been well-documented. The interplay between the NRF2 signaling pathway and processes such as endoplasmic reticulum (ER) stress, unfolded protein response (UPR), and autophagy plays

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a crucial protective role. A deeper understanding of NRF2's role in the modulating these pathways is necessary to develop novel approaches for improving chemotherapeutic efficacy. This article discusses the significance of the NRF2-KEAP1 pathway in preventing/promoting cancer and resistance mechanisms to various chemotherapeutic agents, with a focus on the complementary effects of antioxidants via NRF2-mediated signaling pathways. This study aims to provide a molecular basis for targeting NRF2 *via* inhibitors/activators as promising therapeutic strategies to overcome chemo-resistance.

Keywords: NF-E2-related factor 2; drug resistance; reactive oxygen species; autophagy; unfolded protein response

1. Introduction

Cytotoxic chemotherapy (CTX) is repeatedly employed for early-stage cancers; primarily serving to monitor further spread [1]. In reality, adjuvant CTX is the principal approach in anti-cancer therapy. It involves a wide spectrum of medications with influential cytotoxic outputs that beneficially, though not exclusively, target the rapidly dividing tumor cells [2,3]. Despite remarkable achievements in cancer treatment over the last decade, failure of cancer chemotherapy and/or resistance to new anticancer agents persists, leading to tumor recurrence and metastasis, poorer prognosis, and emerging as a primary obstacle in cancer treatment[4].

The chemo-resistance can be pre-existent (primary resistance) or acquired (secondary resistance), governed by the molecular characteristics of an individual cancer. Primary resistance may be identified early at diagnosis when tumor cells do not initially respond to classical chemotherapeutic agents [5]. On the contrary, secondary resistance may emerge following chemotherapy [6]. Consequently, it is crucial to comprehend molecular systems of cancer, carcinogenesis, and chemo-resistance mechanisms to develop efficient and appropriate care procedures for anticancer treatment. Based on current knowledge, the molecular patterns of chemotherapy insensitivity are associated with DNA repair, proto-oncogenes, anti-oncogene, genes, autophagy, epithelial mesenchymal transition (EMT), tumor cell survival, transporter pumps, mitochondrial alteration, redox controlling complex, and exosomes [7-10] , as outlined in (**Table1**).

Solid tumors are the most common type of tumor affected by cancer hypoxia-induced responses associated with genomic imbalances, which results in increased production of reactive oxygen species (ROS) and abnormalities in damaged DNA re-synthesis pathways [11]. The ROS imbalance under these circumstances, can activate the autophagy pathway through either endoplasmic reticulum (ER) stress or unfolded response protein (UPR) approach, and induces chemoresistance associated with cell cycle arrest and intensifying EMT or cancer stem-like cells [12]. Essentially, autophagy plays an underlying role in cellular viability and survival by eliminating aggregated or misfolded proteins and damaged cellular organelles [13]. The recruitment of autophagy in cancer therapy can play a dual role. Initially, it plays a pro-death role by eliminating transformed cells and damaged cell compartments. However, in in later stages, it plays a pro-survival role by providing protection against hypoxic stress, energy deficits, and chemotherapeutic medications associated with chemo resistance [14].

Autophagy as a multi-step process involved in scavenging damaged cellular components (such as proteins and organelles), engages approximately 40 proteins called autophagy-related proteins (ATGs) [15]. These ATGs are responsible for the formation of autophagosomes, which are double membrane structures that remove their contents upon fusion with lysosomes [16,17]. Initiation, nucleation, elongation, maturation, and fusion are the four phases of the autophagy process [18,19].

In normal biological processes, autophagy maintains cellular health by recycling damaged organelles and proteins, fostering cellular homeostasis, and adapting to stress.[20,21]. Conversely, dysregulation of autophagy is implicated in various pathological conditions. For instance, neurodegenerative diseases such as Alzheimer's and Parkinson's arise from aggregated proteins due to flawed autophagy. Cancer displays a complex relationship with autophagy—promoting tumor

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survival under stress while also preventing tumor initiation. Recognizing autophagy's role in both physiological balance and disease progression unveils potential avenues for therapeutic interventions and disease management[22].

Both in vitro and in vivo studies reveal that oncogenic activation, intrinsic stresses of tumor cells, and extrinsic pressures from the tumor microenvironment (TME), collectively contribute to an increase in misfolded protein levels in the ER and subsequent activation of the UPR pathway. The Unfolded Protein Response (UPR) is coordinated by three proteins located within the endoplasmic reticulum (ER) membrane: activated transcription factor 6 (ATF6), protein kinase RNA-like ER kinase (PERK), and serine/threonine-protein kinase/endoribonuclease inositol-requiring enzyme 1α (IRE1α) [22]. Once initiated, UPR signaling can lead to either cellular adaptation to stress or cell death, depending on variables such as cell type, the specific stress trigger, and the duration and intensity of cellular stress[23]. Proliferating cancer cells might utilize different aspects of the UPR to enhance their existing oncogenic mechanisms for resisting chemotherapy[24]. The UPR has a dual function in the progression of cancer. Initially, it acts as a survival mechanism, enabling cancer cells to maneuver the challenging tumor microenvironment by managing issues like misfolded proteins and limited nutrients. This adaptive reaction supports the survival and adjustment of tumor cells[25]. Conversely, prolonged UPR activation can drive cancer progression. Excessive UPR signaling has the potential to stimulate tumor growth, angiogenesis, and resistance to treatments. Furthermore, UPR-induced inflammation and microenvironment changes can facilitate tumor invasion and metastasis, contributing to aggressive behavior. The paradoxical nature of the UPR underscores the intricate interplay between its safeguarding and harmful effects in the context of cancer[26]. The UPR has emerged as a therapeutic target for the treatment of cancer, given its over-activation in cancer compared to healthy, non-proliferative cells.

Still, cancer-originated hypoxic niches are able to additionally stimulate a large proportion of leader antioxidant gene directors, including the nuclear factor erythroid 2-related factor 2 (NRF2), a family of transcription factors [27,28], existing in various tumors with chemo-resistant phenotypes [29-31]. Previous studies focused on the activators of NRF2 members and their chemo-preventive functions suggest that NRF2 has both have a dark/ negative and light/positive side. The positive aspect shields cells against external stress factors and is deliberately activated to safeguard organisms from diverse diseases. In a similar manner to how NRF2 guards' healthy cells against injury, it can also shield malignant cells. As cells undergo transformation, they encounter numerous stressors, and excessive activation of NRF2 can aid this transformation, supporting cancer cells' growth, dissemination, and resistance to treatment [32,33]. Consequently, research indicates that inhibiting NRF2 may sensitize cancer cells to chemical treatments[34].

Given the inconclusive findings on the role of NRF2 in cancer, a clear picture of NRF2 is necessary to assist researchers in clarifying this intricate arrangement of antioxidant regulation pathways in tumor progression. In addition, it is also essential to define when NRF2 is triggered or repressed in different environments or how it can be affected by the influence of diverse stimuli [35]. In the following parts of the current review, we will explain the complementary effects of antioxidants *via* NRF2-mediated signaling pathways in more detail, in addition to considering the interplay between oxidative stress/redox regulatory networks, autophagy, and UPR-dependent chemo-resistance pathways.

1.1. The Family of Nuclear Factor (Erythroid 2)-Like (NRF) Transcription Factors

Among redox-responsive transcription factors (TFs), NRF2 stands out as one of the most crucial controllers of the cellular defense mechanisms against xenobiotics and oxidative stress [36]. The NF-E2-like BZIP Transcription Factor 2 (*NFE2L2*) gene encodes the NRF 2, which belongs to the cap 'n' collar basic region leucine zipper (CNC-bZIP) family with four closely related members, including NRF 1, NRF 2, NRF 3, and p45 nuclear factor erythroid-derived 2 (NFE2) protein [37]. These protein members feature seven functional NRF2-ECH homology (Neh) domains with high evolutionary conservation, each playing specific roles in modulating its transcriptional activity. The Neh1 region, which holds a bZIP binding sequence, engages with members of the small musculoaponeurotic

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fibrosarcoma (sMAFs) family (MAFF, MAFG, and MAFK), along with other bZIP motifs. This interaction enables the binding to functional antioxidant response elements (AREs), prompting the initiation of transcriptional gene expression. On the other hand, the Neh2 domain comprises two distinct binding sequences, namely DLG and ETGE. These sequences independently form dimers with the Kelch domains of Kelch-like-ECH-associated protein 1 (KEAP1), ultimately facilitating the degradation of NRF2 through UPR-mediated processes.[38,39]. The Neh3-5 transcription activation domains interact with different elements of the core-transcriptional machinery.

Two highly conserved redox-insensitive motifs in Neh6-domain, namely DSGIS and DSAPGS, form dimers with β-transducin repeat-containing E3 ubiquitin protein ligase (β-TrCP), inducing NRF2 degradation in oxidative stressed cells [40]. Neh7 domain of NRF2 characteristically heterodimerizes with retinoid X receptor alpha (RXRα) and suppresses the NRF2 function [41]. These domains regulate NRF2 integrity and the trans-activation of the downstream target genes across transcriptional and post-transcriptional modifications along with post-translational directive pathways against different lesions [42]. All four members of the NRF family are characterized by a unique N-terminal 43-aa CNC domain and play crucial roles during embryo development and in response to environmental stresses [37,43]. However, recent studies have identified novel NRF2 target genes with a number of additional features of NRF2 beyond its redox-managing roles, including regulation of inflammatory responses, cell metabolism, autophagy, proteostasis, ER stress, and the UPR, especially in tumorigenesis [44-47]. Recognizing the diverese features and functions of NRF2 and its emerging activities will pose additional challenges beyond exploring its potential in NRF2-targeted anti-cancer drugs.

The expression profiles of NRF transcription factors vary significantly based to tissue specificity. While *NRF1* and *NRF2* exhibit widespread expression, *NRF3* is notably confined to the placenta and liver. Additionally, NF-E2 is specifically limited to megakaryocytes, mast cells, erythrocytes, and hematopoietic progenitors. [48-50]. It appears NRF1 assists in the the proteasome transcriptional bounce-back response to proteasome blocker processing [51]. The Activated NRF1 accumulates, migrates across the ER membrane, and then acts as a nuclear transcription factors following de-glycosylation and partial proteolytic cleavage processing in the nucleus [52]. However, its proteasome-mediated degradation activity and transcriptional capabilities have not been fully elucidated [53].

It is now established that NRF1 plays an important role in the development of resistance to cancer treatments[54,55]. Apparently, NRF1 protects tumor cells from proteotoxicity, which is enhanced by antitumor proteasome blockers [56]. Amongst the NRF transcription factor members, recent studies on NRF3 protein have demonstrated that it drives key functions of 20S in tumor proliferation and progression of malignant tumors by down- modulating the tumor suppressor proteins p53 and retinoblastoma-associated protein (pRB) over driving the 20S proteasome in different tumor cell types [57-60]. Moreover, these actions directly contribute to the subsequent metastasis and induction of angiogenesis in malignant tumors [61].

1.2. Deciphering the transcriptional NRF2 -regulated target genes

The NRF2 function is meticulously regulated. Despite the binding of activated NRF2 to DNA, it has been observed through DNA transcription profiling that not all genes in close proximity to the activated NRF2 are transcriptionally controlled by NRF2 attachment [62]. These NRF2 target genes need the cooperative recruitment of NRF2 and NRF2 interactive co-activators, such as cofactors and transcription factors or mediator proteins for a full stimulation [63]. The small MAF-TFs, namely MAF-F, MAF-G, and MAF-K, interact with transcriptional NRF2 across the associated bZIP motifs to make NRF2/ MAF heterodimer identify the ARE and trigger transcriptional regulatory function of NRF2 about genes encoding detoxification enzymes [64].

Transcriptional modulator BTB and CNC homology 1 (BACH1) is required to repress heme oxygenase (HO)-1 gene transcription, which goes against NRF2/ sMAFs interplay in the upstream promotor region and target NRF2-dependent transcription NAD(P)H: quinone oxidoreductase1 (NQO1) [65,66]. The upregulation of the *NRF2*/*HO-1* binding results in *HO-1* expression and requires

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the deactivation of *BACH1*[67,68]. Intrestingly, NRF2- activating transcription factor 4 (ATF4) dimers bind with NRF2 at ARE sites to activate HO-1 transcription as well. Physical Interaction of the Activator protein 1 (AP-1) subunit c-Jun with NRF2 stimulates NRF2-driven transcriptional inducers, although another AP-1 subunit c-FOS can inhibit favorable NRF2 activity [69]. The collaboration between the cAMP-response element binding protein (CREB)-binding protein (CBP) and its co-activator p300 is utilized to jointly bind to the antioxidant response element (ARE) by employing the transactivation domains Neh4/5 of NRF2. This interaction plays a role in facilitating the activation of gene transcription. Both histone acetyltransferases CBP and p300 cause chromatin decompaction to be conducive to the employment of the transcription apparatus [68,70].

Nonetheless, ATF3 mediator can interact with CBP, inhibiting the binding of NRF2 and repressing transcription arising from the NRF2–CBP complex. Remarkably, the removal of *Atf3* increases NRF2 destruction via overexpression of the *KEAP1* gene and the loss of human DJ-1 in the H157 NSCLC squamous cell line [71]. Hence, ATF3 functions as a potential regulator, either positively or negatively, involved in the modulation of NRF2 activity [72,73].

Additional transcription complex co-regulators, including SIRT6, an NAD^+-dependent histone deacetylase, the ATPase subunit of the chromatin-remodeling complex SWI/SNF, RAC3, a co-activator linked to receptors, CHD6, a chromodomain helicase DNA-binding protein, BRG-1, a gene associated with Brahma, and subunit 16 of the mediator involved in RNA polymerase II transcription, have the capability to activate NRF2, thereby influencing the transactivation process of genes that are targeted by NRF2 [39]. Nevertheless, the actual implication of such interactions are not yet fully understood. The nuclear receptors estrogen receptors α and peroxisome proliferator-activated receptor gamma (PPARγ) can selectively bind to NRF2, inhibiting its transcriptional activity [74]. Notably, gene expression profiles from the livers of Keap1 knockout/knockdown and Nfe2l2-null mice relative to the corresponding control wild-type mice in a gene dose response experiment, demonstrated that *Nrf2* activity is correlated with the expression level of *Nrf2*[75]. A comprehensive understanding of the gene transactivation orchestrated by NRF2 necessitates a concentrated examination of the synergistic interplay and potential rivalry between NRF2 and various other categories of transcription factors and co-regulators that are intricately linked to both ARE sequences and similar ARE-like regions.

1.3. NRF2- driven response to oxidative stress and drug metabolizing

Antioxidant detoxification and drug metabolizing control *via* transcriptional activation of ARE-mediated β-globin genes are recognized as significant emerging activities of NRF2 as a well-known NC-bZIP TF [76]. Recent studies have shown that the activation of antioxidant cytoprotective genes over the Nrf2/antioxidant response component in response to cellular oxidative stress results in a complex of collaborating enzymes complicated in phase I, II, and III biotransformation reactions and the removal of oxidative inducers to maintain homeostasis [77-80]. Phase I reactions of xenobiotic metabolism correspond to oxidoreductase and hydrolysis, catalyzed by NQO1, aldo-keto reductases (AKRs), adenine dinucleotide phosphate (NADPH)–oxidoreductases cytochrome P450s (CYPs), and carbonyl reductases (CBRs) as well as aldehyde dehydrogenase 1 (ALDH1) enzymes [81]. Enzymatic conjugation, UDP-glucuronic acid production enzymes UDP-glucuronosyltransferase (UGT), glutathione S-transferase (GST), and heme oxygenase 1 (HO-1) are all included in Phase II. Phase III mechanisms of xenobiotic conjugation and transport primarily revolve around the accumulation of non-toxic or conjugated metabolites subsequent to phase II reactions. These mechanisms predominantly involve drug efflux pumps such as the breast cancer resistance-related protein (BCRP/ABCG2), multidrug-resistance-associated-proteins (MDR), and ATP-binding cassette G8 (ABCG8) [82,83].

Conventional antioxidant defense systems triggered by NRF2-driven enzymes participate in the biosynthesis of reduced glutathione (GSH) (glutathione synthetase (GSS)) and its usage and recycling (glutamate-cysteine ligase catalytic (GCLC) and modulator (GCLM) subunits)[84]. In addition, several other antioxidant enzymes, involved in the removal of reactive oxygen and nitrogen products (ROS/RNS) (glutathione s-transferases, peroxiredoxins, superoxide

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dismutase, thioredoxins, and thioredoxins reductases) are all known target genes of NRF2 [85]. play a crucial role in maintaining normal homeostasis disturbed by redox signaling. They are instrumental in addressing various disorders characterized by oxidative stress, including neurodegenerative and cardiovascular diseases, autoimmune disorders with metabolic syndrome, and cancer. [86].

Studies suggest that the induction of the NRF2 signaling pathway is a powerful approach in tumor suppression, and a feasible strategy in anticancer therapy [87,88]. Furthermore, pharmaceutical induction of NRF2, can reduce carcinogenesis and perform a protective function compared to tumor initiation in normal cells. The absence of NRF2 decreases prompt GST expression, leading to an increases in ROS level, resulting in DNA damage and a predisposition to carcinogenesis [89]. Besides, other investigations suggest that NRF2 may also support cancer development. For example, there is a focus on developing NRF2 inhibitors to reverse the resistance of cancer cells to chemotherapy. Simultaneously, researchers are exploring Nrf2 activators as potential safeguards against the harmful impacts or undesirable outcomes of chemotherapy treatments [90].

1.4. NRF2 signaling pathway in cancer

The significance of NRF2 in cancer is widely recognized. It is crucial to understand its negative regulator, KEAP1, which modulates NRF2 to decrease its cellular expression and effectively control metabolic balance [91]. The KEAP1 activity is closely correlated with cellular levels of NRF2 protein after normal or low/moderate responses to stressful situations to monitor cellular antioxidant responses, as well as detoxification responses involved in cancer prevention and treatment [92].Understanding these regulators would enable researchers to channel NRF2's footprint into a more targeted approach aiming to completely eradicate tumors, while also addressingits pro-oncogenic effects, most of which are associated with the "dark side" of NRF2, clearly linked to the metastatic behavior of tumor cells [93].

Numerous studies have shown that the activation of NRF2 preserves the health of cells exposed to diverse toxic components and illnesses; it has also been observed that the over-activation of NRF2 promotes tumor development and protects tumor cells from oxidative injury, which can further induce chemo-resistance [94]. The elevated levels of NRF2 observed in cancer contributes to an increased expression of key metabolic enzymes including transketolase (TKT), phosphogluconate dehydrogenase (PGD), glucose 6-phosphate dehydrogenase (G6PD), and several others [95]. This heightened activity of glucose metabolic enzymes promotes the production of purine and amino acids, along with the regeneration of the NADPH pool through the pentose phosphate pathway (PPP). Consequently,, there is a reconfiguration of metabolic pathways to faciliate cellular growth and enhance antioxidant capacity [96].

As a key regulator in carcinogenesis, the cell cycle is closely linked to Nrf2 over-activation, as Nrf2 deficiency leads to arrest in the G2/M phase of the cell cycle. It appears that Nrf2 is a controller in the regulation of the cell cycle through the phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) signaling [97]. Some studies have indicated that the over-expression of NRF2 induces the phosphorylation of AKT, glycogen synthase kinase-3 (GSK3), PPP, and KRAS activation[98,99]. In addition, cooperation between the PI3K/AKT and KRAS/MAPK pathways can lead to an increase in the anabolic pathways efficiency, the inhibition of the apoptosis, and induce survival and self-renewal inducement in cancer stem cells (CSCs) by anti-apoptotic factor B-cell lymphoma 2 (Bcl-2) [100]. These mechanisms contribute to the development and progression of cancer[101].

Furthermore, the activation of Nrf2 is associated with the inhibition of chronic inflammation, a factor linked to cancer[102]. Inthe absence of Nrf2, certain pro-inflammatory factors such as inducible nitric oxide synthase (iNOS), tumor necrosis factor-alpha (TNF-α), and cyclooxygenase-2 (COX-2), are increased significantly [103]. The iNOS can produce nitric oxide, which contributes in inflammation and tumor development[104]. It also can cause mutagenesis and DNA degradation [105]. The TNF-α is one of the main cytokines regulating the progression of inflammation through different signaling pathways [105,106]. Additionally, Cox-2 serves as another regulator of inflammatory diseases [106] (**Figure 1**).

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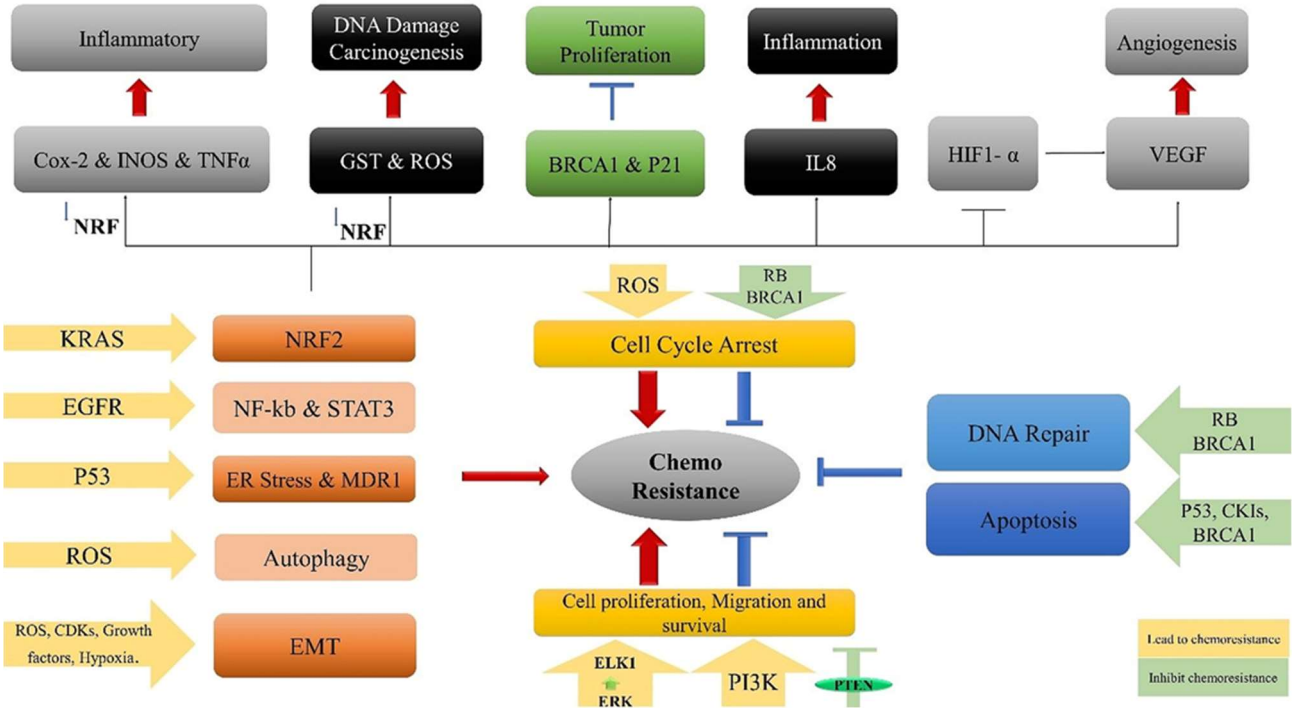

Figure 1. NRF-affected pathways. A perspective of the pathways affecting chemical resistance.

Furthermore, Nrf2 regulates the fundamental expression of mouse double minute 2 homolog (Mdm2), a potential repressor of tumor suppressor p53 [107]. Similarly, the overexpression of the transcription factor Nrf2 secondarily down-modulates TP53 and enhances cancer cell self-renewal by inhibiting p53-linked apoptotic death signals [108]. In an investigation involving human refractory ovarian cancer cells, the elevated expression of NRF2 was observed compared to the non-resistant cell line, and NRF2 knockout by siRNA reintroduced drug response. In addition, chemical NRF2 induction delivered a survivability nature to immortalize neuroblastoma cell lines responding to tumor medications such as etoposide, cisplatin, and doxorubicin [109,110]. Based on these findings,, Cho and his team confirmed that the knockdown of NRF2 through siRNA treatment enhanced the cisplatin sensitivity in ovarian cancer cells [109]. Likewise, Long-term stimulation of NRF2 has been found to impair efficacy of combined drug and radiation treatment in human respiratory tract cancer cells. Conversely, lower levels of NRF2 increased the cellular response to ionizing radiation and cytotoxic drugs [111]. The above results suggest that Nrf2 function alone or in combination with complementary drugs can be considered a productive method to improve the response of metastatic cells to chemotherapy. Moreover, recent investigations highlight the role of Nrf2 in malignancy, where functional Nrf2 promotes lung cancer metastasis by preventing the degradation of the heme-binding Bach1 transcription regulator [112].

The overproduction of NRF2 triggers cell growth and metastasis in breast cancer by activating the RhoA gene expression along with its downstream effectors [113]. The significant role of NRF2 in proliferation and invasion is also observed in hepatocellular carcinoma, where it regulates the post-transcriptional expression of target genes such as metalloproteinase-9 (MMP-9) and BCL-XL transcripts [93]. Recent findings have highlighted that, beyond facilitating tumor advancement, UPR activation can also play a role in the development of chemo resistance (as depicted in **Table 1**) [114-117]. Silencing all three branches of the UPR has been linked to the restoration of sensitivity in previously resistant cancer cells [116,118,119]. Rapidly dividing tumor cells might exploit distinct UPR branches to complement their pre-existing mechanisms of chemo-resistance. Furthermore, the targeted activation of a specific UPR arm may be intertwined with other inherent mechanisms of chemo-resistance [24].

Antioxidants play a complex role in cancer therapy, resembling a double-edged sword. While they can potentially protect healthy cells from the damaging effects of treatments like chemotherapy

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and radiation by neutralizing harmful free radicals, they might also inadvertently shield cancer cells from these therapies, reducing their effectiveness. This duality underscores the need for a balanced approach when considering the use of antioxidants in cancer treatment strategies [120]. This regulation exhibits the dual character of ROS: at low concentrations, it acts as a critical second intracellular messenger in various signal transduction pathways, whereas at high concentrations, through a change in gene expression, cells try to confront stress by converting to antioxidant response [27].

As mentioned earlier, the activation of NRF2 signaling has gained attention for its potential to mitigate the adverse effects of chemotherapy. This pathway plays a protective role by shielding cells from oxidative harm. However, inhibiting oxidative-induced cell death through NRF2 activation can lead to the development of chemo-resistance in cancer cells. Evidently, NRF2 might contribute to the promotion of tumor-initiating cell lineage, consequently giving rise to chemo resistance. [35]. Increased NRF2 expression has been studied in various cancer types, including head and neck, lung, epithelial, gastric, and pancreatic cancer [93,121,122]. It has been found that elevated NRF2 expression can lead to resistance to radiation, 5-fluorouracil, and cisplatin, possibly through the induction of antioxidants [123]. Therefore, there may be a need to consider inhibiting the NRF2 pathway during chemotherapy [34].

Table 1. Molecular Mechanisms involved in chemo-resistance.

Underlying molecular mechanism	Cellular effect	Reference
Transporter pumps (ABC proteins, SERCA, V-ATPase)	These proteins exhibit elevated expression levels in chemo-resistant cancer cells and play a role in the development of drug resistance.	[124-126]
Oncogenes EGFR	The overexpression of EGFR triggers the activation of NF-κB and STAT3, which subsequently leads to the development of chemo-resistance and unfavorable treatment outcomes.	[127]
KRAS	Oncogenic KRAS promotes drug resistance via upregulation of the cell protective stress response gene, NRF-2, at the transcriptional level.	[128]
(PI3K)/Akt	AKT involves in apoptosis, migration, and proliferation.	[129]
NF-κB	Following activation, NF-κB translocates to the nucleus, elevating the expression of BCL-2, BCL-XL, XIAP, survivin, and AKT, thereby contributing to accelerated tumorigenesis, increased	[130]

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	aggressiveness, drug resistance, and induction of EMT.	
ERKs	ERKs are recognized for their role as activators of various transcription factors, including ETS Like1, along with downstream protein kinases. These factors are closely linked to processes such as cell proliferation, drug resistance, and apoptosis.	[131]
Oncogenic Viruses	Viral onco-proteins contribute to chemo-resistance through multiple mechanisms, including the regulation of cellular transporters and drug targets, modulation of signaling pathways involved in drug-induced cell death responses, and activation of pathways that counteract the effects of drugs.	[120]
Rb	Oncogenic p53 causes chemo-resistance of cancer cells by increasing the expression of MDR-1.	[132-137]
CKIs	These mechanisms involve inducing cell cycle arrest and activating DNA repair processes	[138-140]
PTEN	Increase apoptosis, regulating cell cycle progression.	[141,142]
BRCA1	Reduction of cell proliferation, migration, survival and cell size, Regulating transcription, cell cycle checkpoint, DNA repair, and apoptosis.	[143-146]
Mitochondrial alteration SERCA	Bcl-2 and Bcl-xL contribute to heightened drug resistance, while reducing their expression enhances the cytotoxic impact of cisplatin and gemcitabine. Moreover, the level of survivin expression was found to be linked to the degree of cisplatin resistance in gasteric cancer cells.	[147]
V-ATPase	Somatic mutations occurring in the mitochondrial genome (mtDNA) of cancer cells lead to impaired	[148]

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	mitochondrial function, which in turn contributes to the development of chemo-resistance.	
DNA repair	BER and NER can confer the resistance to chemo drugs that target DNA. RAD51, a crucial participant in homologous recombination during double-strand break (DSB) repair, being overexpressed, serves as a marker for resistance to Cisplatin (CDDP) in non-small cell lung cancer (NSCLC). Similarly, elevated expression of ERCC1, a component of the nucleotide excision repair (NER) pathway, is associated with resistance to CDDP in both human hepatocellular carcinoma (HCC) cell lines and specimens.	[149-151]
Autophagy	In tamoxifen-resistance breast cancer cells, SAHA, as a HDAC inhibitor, can induce autophagic cell death and reduce tumor growth. Despite the challenges about the anticancer and pro-survival function of autophagy, in vitro and in vivo research has been more confirmed that autophagy could be considered as a facilitator of cancer chemo-resistance. In NSCLC cells, autophagy inhibition using Chloroquine, before paclitaxel treatment, prevents drug resistance.	[14,152,153]
UPR	CSCs and actively dividing tumor cells might exploit distinct branches of the UPR to reinforce their pre-existing mechanisms of chemo-resistance. Notably, the suppression of all three UPR branches—GRp78, ATF6, ATF4, and XBP1s—has shown a correlation with the restoration of sensitivity in chemotherapy-resistant cancer cells.	[24,116-119]

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EMT	EMT has been identified as a promoter of chemo-resistance against the DNA alkylating agent cyclophosphamide and the DNA synthesis inhibitor gemcitabine. Specifically, the attenuation of Snail or Twist has been linked to increased sensitivity to chemotherapy.	[154]
Cancer stemness	Cancer stem cells (CSCs) resist chemotherapy by increasing the levels of P-glycoprotein, ABCG2, BCL-2, and survivin. Recent findings highlight NRF2's role in preserving stemness, intensifying tumorigenicity, and initiating chemo-resistance within CSCs.	[155,156]
Regulatory redox network	The mechanisms of ROS-mediated acquired chemo-resistance include autophagy, ER stress, overcoming cell cycle arrest, and enhancing epithelial to mesenchymal transition or cancer stem-like cells. Numerous chemotherapy agents, including cisplatin, doxorubicin, etoposide, paclitaxel, and bortezomib, induce cancer cell death by elevating ROS levels. Adjusting intracellular antioxidant levels holds potential therapeutic benefits but can be complex. While antioxidants may impede chemotherapy efficacy by scavenging ROS, they can also trigger chemotherapy-related toxicity, highlighting a delicate balance.	[12,120,157]

2. Redox regulatory network involved in the induction of autophagy/UPR and tumor chemo-resistance

The activation of UPR relieves ER stress by reducing protein translation to lessen protein load in the ER, increasing the translation of chaperones to facilitate the ER protein folding, and removing misfolded proteins [158]. Sustained UPR activation induces apoptosis, but tumor cells can bypass the apoptosis and use the UPR for tumor proliferation. Recent findings reveal that UPR is also involved in the chemo-resistance of the tumor cells [24]. Based on several findings, multiple elements of the

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UPR are associated with advanced tumor stage and resistance to chemotherapy [24,159,160]. In this context, the overexpression of *XBP1* is a significant event associated with chemo-resistance and short-term survival in lymphoma [161]. In the case of ABCs, as major contributors to chemo-resistance, ABC activity can be diminished by inhibiting *GRP78* which also reduces the antioxidant response due to ROS accumulation. Recently, it has been shown that IT-139, a small inhibitor of the GRP78 molecule, can sensitize chemically resistant PDAC cells to gemcitabine [162]. *GRP78*-mediated ER homeostasis is associated with the activity of specificity protein 1 (SP1). SP1 inhibits homeostasis, negatively affecting the UPR and inducing cancer cell death. This modulation occurs through the regulation of NRF2 antioxidant responses and ABC transporter activity by inhibiting *GRP78*-mediated ER homeostasis. [163].

The PERK pathway also exerts its adaptive effect(s), which includes transient inhibition of eIF2α and antioxidant response by inducing the transcription factor NRF2 [164-166]. NRF2, which governs the response to oxidative stress, functions downstream of PERK. This regulatory role can extend to influencing the expression of the ABCC subfamily. While NRF2 predominantly functions as a tumor suppressor, heightened activity of its antioxidant response elements can enhance the survival of both normal and cancerous cells (**Figure 2**) [167] .

Additionally, studies have shown that cells experience an increase in mitochondrial ROS, metabolic changes, and the accumulation of free radicals during hypoxia, leading to metabolic stress. Under the hypoxic conditions, HIF-1α protein accumulation, the central regulator of the cellular response to hypoxia, activates the UPR pathway as a mechanism of adaptation of tumor cells, causing tumor growth and resistance to chemo and radiation therapy [168]. Indeed, hypoxia induces the PERK/eIF2α/ATF4 axis, with PERK ultimately leading to phosphorylation and subsequent activation of the FOXO-1 (anti-apoptotic forkhead box O-1) as well as pro-autophagic components. The up-regulation of autophagy, along with the suppressed apoptosis, make cells resistant to chemotherapeutic drugs (**Figure 2**) [169]. In contrast, prolonged activation of UPR pathway, triggers cell death mechanisms once environmental ER stress is not relieved. Under these conditions, different pathways that lead to cell death will be initiated, limiting the progression of cancer. There is substantial evidence that ROS-induced autophagic cell death may play an important role in these pathways; as ROS can regulate the expression of ATGs, such as ATG4 and Beclin1 [157].

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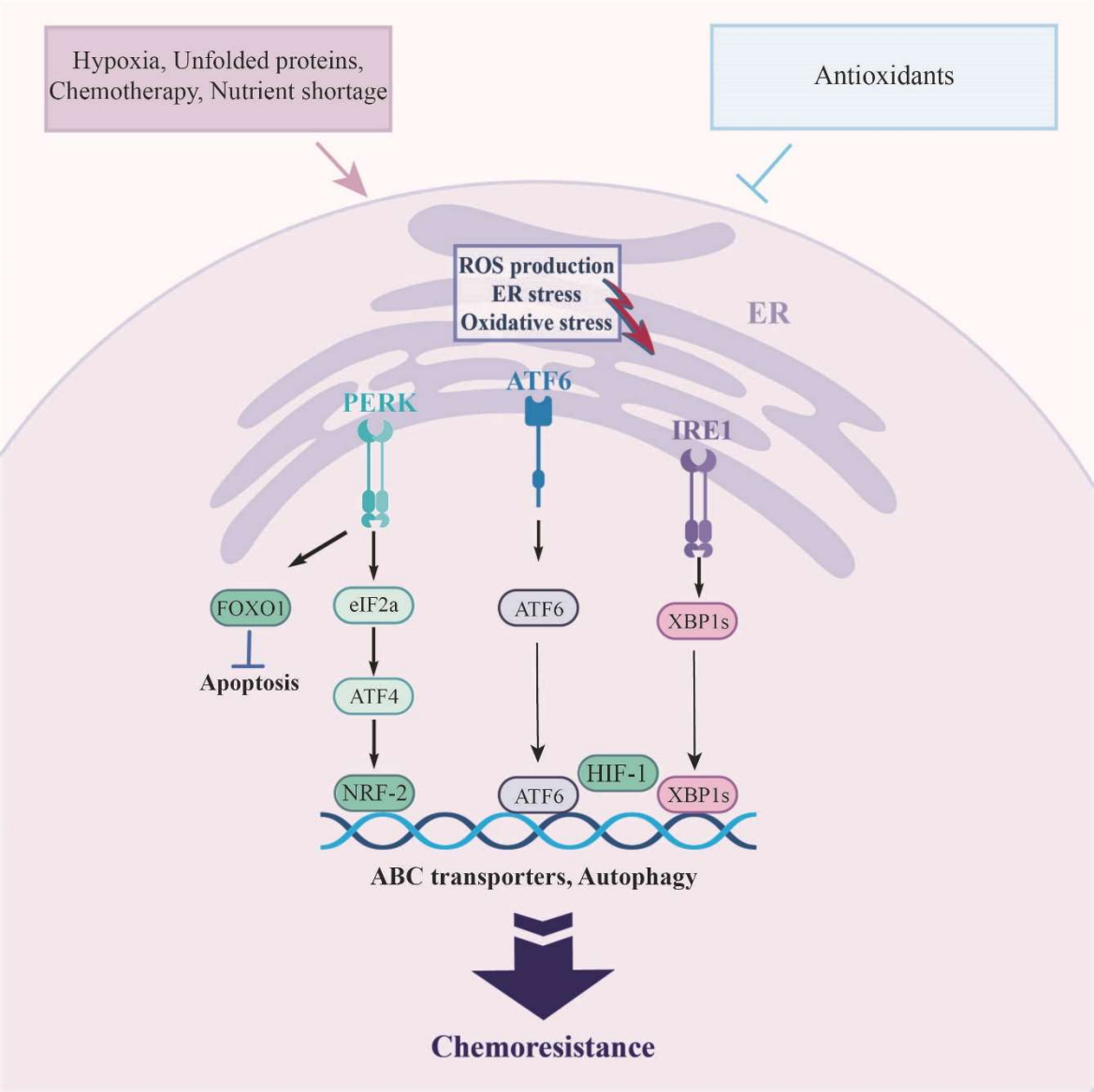

Figure 2. Schematic view of oxidative stress, UPR sensors, autophagy, and drug resistance. In oxidative stress, the UPR sensors cooperate in chemo-resistance induction. PERK/ eIF2α/ATF4 axis leads to activation of the anti-apoptotic factor Fork-head box O-1 (FOXO-1) and transcription factor NRF2, which regulates the expression of ABC transporters. Increased autophagy flux and the inhibition of apoptosis pathway makes cells resistant to chemotherapy agents.

Nonetheless, ROS exhibit a dual nature in the context of cancer. The increased ROS levels contribute to the enhanced growth of cancer cells by triggering signaling pathways, such as the PI3K/AKT and up-regulation of their antioxidant components, which consequently leads to the development of drug resistance within cancer cells [11]. Furthermore, high levels of ROS may guide tumor cells toward different pathways of cell death and restrict their expansion [170]. Accordingly, anti-cancer therapies that increase ROS or inhibit antioxidant levels are considered as novel treatment strategies in this context.

The utility of chemo-drugs, such as cisplatin, doxorubicin, and paclitaxel with the ability of inducing ROS levels inside the cancer cells, is considered an appropriate option for curing cancers by triggering cell death-related pathways. Amongst these pathways, autophagy ROS-induced cell death plays a considerable role [171]. Studies have shown that antioxidants can inhibit the autophagy flux and indicate a direct involvement of ROS in inducing autophagy. Autophagy has been proven as a significant degradation system for eliminating harmful protein components from the endoplasmic reticulum (ER) and is capable of breaking down a broader array of substrates [172].

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Recent studies have shown that ROS is necessary for autophagy induction. ROS oxidizes the cysteine protease ATG4, which results in ATG8 lipidation and the formation of autophagosomes. These reactive species also regulate autophagy by the activation of TFEB-nuclear translocation. High levels of ROS activate adenosine monophosphate-activated protein kinase (AMPK) and mitogen-activated protein kinase (MAPK), inducing autophagy [173]. Autophagy is thus a strategy exploited by tumor cells to get adopted to tumor environment, resulting in chemo-resistance development [174].

Regarding this matter, a study conducted on breast cancer cell lines revealed that the application of carnosol polyphenols resulted in cell death through a process involving ROS-triggered autophagy followed by late-stage apoptosis[175]. New evidence suggests that autophagy inhibitors and antioxidants may be able to prevent cancer cell death [17,176,177]. Consistently, data obtained about utility of resveratrol or psoralen showed that human colon cancer (COLO 201, HT-29) and human lung cancer (A549) cells die by increasing ROS accumulation and autophagy levels, respectively. However, the use of 3-MA or antioxidants reverse these effects [178].

This hypothesis can also be exemplified by studies conducted on glioma cells, as demonstrated that after treatment with polycyclic ammonium ion sanguinarine, H_2O_2 could increase the autophagic cell death. In addition, ROS can induce the expression of SQSTM1/p62 and Beclin1/ATG6 genes *via* the NF-κB, and thus can regulate autophagy inside the malignant cells [178] . Although autophagy can play a suppressive role durig the early stages of cancer progression, it can also increase cell survival and metastasis, thus protecting tumor cells against environmental and drug stresses [179].

Conclusively, ROS act as a double-edged sword, with both sides being used therapeutically. There is still much debate about the use of antioxidant supplementation or its inhibition to modulate ROS levels in cancer therapy. Due to the effective role of the UPR pathway and autophagy in maintaining cellular homeostasis, resistance and survival of cancer cells, further studies are strictly needed to target these two pathways in modifying ROS content during cancer.

2.1. The cross talk between different arms of UPR-autophagy in drug resistance and cancer cell survival

Despite the significance of autophagy and ER stress in multiple human illnesses [180-182], the interplay between autophagy and the UPR is still unclear. Recently it was shown that UPR's signaling arms strongly correlate with autophagy. We discussed in detail the interplay between UPR signaling arms with autophagy, principal molecular mechanisms, and their role in drug resistance in the following section.

2.1.1. Interaction among IRE1/XBP1s, IRE1/TRAF2/ASK1/JNK, and Autophagy

Activating the IRE1/XBP1s signaling arm of the UPR can be a reliable method to correct impairments of ER proteostasis indicated in different diseases [183]. IRE1 contains two major domains, namely a serine/threonine kinase domain, an endoribonuclease domain [184]. Unconventional splicing of X-box-binding protein-1 (*XBP1*) and regulated IRE1 dependent decay (RIDD) are two downstream mechanisms through which IRE1 primarily exerts its pro-survival effects[185,186]. It should be noted that the IRE1 pathway is actually the most evolutionarily conserved arm of the UPR, as it is identified in almost all eukaryotes [187]. Spliced XBP1 (XBP1s), which is a key transcription factor produced by the IRE1's endoribonuclease activity [188], can bind to the UPR-targeted genes inside the nucleus (e.g., *GRP78*) to accelerate the protein folding capacity and restore cellular homeostasis [185].

As depicted in (**Figure 3**), the IRE1/XBP1s pathway can induce autophagy in three main phases: (i) XBP1s indirectly induces autophagy by operating the expression of Bcl-2 [189-191], XBP1s may trigger autophagy by facilitating the LC3βI to LC3β II conversion, and the overexpression of Beclin-1(BECN) [192,193], and (iii) XBP1s can form a homo- or heterodimer and attach to the *BECN1* gene promoter to up-regulate the Beclin -1(BECN) expression [194]. Accordingly, IRE1/XBP1s axis is believed to be a positive modulator of autophagy with pro-survival effects. Nonetheless, IRE1/XBP1s deficiency has been reported to cause an increase in autophagy and cell survival in a group of amyotrophic lateral sclerosis patients [195,196]. *Xbp1s* deficiency may also lead to the overexpression of Forkhead box O1 (FoxO1) to stimulate neuronal autophagy [197].

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Furthermore, C-Jun NH2-terminal kinase (JNK) is known as a stress-associated protein involved in a vast array of cellular processes [198]. Once the UPR becomes initiated, the adaptor protein tumor necrosis factor receptor-associated factor-2 (Traf2) is recruited by the activated IRE1 and creates the Ire1-Traf2 complex. Afterward, the apoptosis-signal regulating kinase 1 (Ask1) arranges the formation of the Ire1-Traf2-Ask1 complex [199]. Interestingly, the IRE1/TRAF-2/JNK1 axis can operate ER stress-triggered autophagy, as mouse embryonic fibroblast cells deficient in IRE1/TRAF-2 have revealed a significant decrease in the formation of autophagosomes [191]. Pharmacological inhibitors of JNK1 can also suppress autophagosome formation; SP600125 is a good example in this regard [200].

The JNK1 pathway also has a central role in the transcriptional modulation of Beclin-1(BECN) expression. It has been demonstrated that JNK1 is involved in starvation-triggered autophagy by phosphorylating BCL-2, localized in ER, resulting in separation of Beclin-1(BECN) from BCL-2 and subsequent initiation of autophagic flux [201]. In sum, the IRE1/JNK1/c-JUN axis is a pivotal mechanism to induce autophagy. IRE1/XBP1s and IRE1/JNK1 stimulated-autophagy pathways join at BECN. Hence, BECN can be a promising therapeutic target to mediate the ER stress-triggered autophagy in drastic pathological conditions, such as malignancies, cancer drug resistance, and cancer cell survival.

2.1.2. The role of IRE1/XBP1s arm of UPR and autophagy in drug resistance and cancer cell survival

IRE1 modulates irregular splicing of *XBP1* mRNA, as well as the expression of cyclin A1, supporting the IRE1-induced cancer cell growth [202]. High levels of *XBP1s*, which results from increased *XBP1* splicing, have been reported in multiple cancers and represent a poor prognosis [203,204]. For instance, a high ratio of *XBP1s*/*XBP1* has been demonstrated to be strongly correlated with poor prognosis and a shortened relapse period in myeloma patients [205]. Treating multiple myeloma cells with MKC-3946, as an inhibiting agent of IRE1α endoribonuclease activity, desirably results in the repression of *XBP1* splicing and induction of ER-regulated apoptosis in these cells when simultaneously treated with bortezomib. It can be concluded that the IRE1-XBP1 axis is central to the viability of (multiple myeloma) cells, and directing this pathway may lead to anti-tumor effects [205]. Furthermore, we recently presented evidence that simvastatin (Simva), through the activation of the IRE-1 arm of UPR, enhances temozolomide (TMZ)-induced cell death in U87, U251 glioblastoma cells. Moreover, our result revealed that IRE-1 regulated Simva-TMZ mediated autophagy flux inhibition and improved TMZ efficacy[22] .

The involvement of XBP1s in triggering relapse of triple-negative breast cancer (TNBC) tumors *in vivo* has also been observed. After doxorubicin therapy, MDA-MB-231 xenografts initially experience a decrease in tumor size, followed by tumor regrowth once the therapy is stopped [24,206]. When *XBP1* is suppressed in MDA-MB-231 xenografts, the regrowth of tumors following doxorubicin withdrawal is inhibited. Additionally, the use of the MKC8866 inhibitor to reduce IRE1 RNase activity in MDA-MB-231 cells prevents regrowth after paclitaxel withdrawal, suggesting a correlation between XBP1s signaling and tumor regrowth [207].

In addition to *XBP1s*, *GRP78* overexpression has been identified to be strongly associated with chemotherapy impairment through certain molecular mechanisms [208,209]. Interestingly, during ER stress, GRP78 is capable of becoming anchored as a cell surface receptor [210]. This novel receptor can activate the PI3K/AKT signaling pathway and inhibit the transforming growth factor (TGF-β) pathway, to induce cell survival and growth [211]. Previous studies have suggested that upregulation of *GRP78* may contribute to chemo resistance of a group of cancers, such as breast cancer, glioblastoma, and other aggressive gliomas [212,213]. This finding proposed that *GPR78* could be considered as a promising link between metabolic alterations and tumor survival. Therefore, targeting GRP78 emerges as a potential approach to overcome chemotherapeutic failure in the coming years.

2.1.3. Cross-talk between the PERK/eukaryotic translation initial factor 2α (eIF2α)/ ATF4/CHOP axis and autophagy

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PERK/eIF2α/ATF4/CHOP pathway constitutes another branch of the UPR. PERK is a serine/threonine kinase is activated through both autophosphorylation and homodimerization upon releasing from GRP78 [214]. Once activated, PERK inhibits protein synthesis by phosphorylating eIF2α, disrupting the attachment of methionyl-tRNA and ribosomes [215]. Subsequently, phosphorylated eIF2α promotes ATF4 translation, aiding the ER in protein folding[216]. Moreover, the overexpressed ATF4 induces the translation of CCAAT/enhancer binding protein (C/EBP) homologous protein (CHOP), which contributes to ER stress-mediated apoptosis and is considered as a marker to evaluate the stimulation of the UPR [217].

In association with autophagy, ATF4 plays a central role inin upregulating ATG12, an essential component of the ATG5-ATG12-ATG16L complex (**figure 3**), and critical for autophagosome elongation [218]. It has also been reported that ATF4 can directly bind to the cAMP response element binding site located in the light chain 3B (*LC3B)* promoter, inducing the expression of LC3B to trigger the autophagic flux [219]. Furthermore, in the context of melanoma, B-RAF proto-oncogene (BRAF)-induced phosphorylation of PERK is pivotal for autophagosome generation[220]. Pharmacological suppression of PERK using GSK2606414, or siRNA-induced blockade of this serine/threonine kinase, significantly reduces the Lc3B II/Lc3 BI ratio [221]. Regarding CHOP, as a powerful transcription factor involved in autophagy, UPR and some other cellular processes, it has been reported that its overexpression induces the expression of ATG5 and BH3-only proteins like Bim and Puma.

Furthermore, CHOP downregulates the expression of Bcl-2,facilitating the release of Beclin-1 from this anti-apoptotic protein [217,222,223]. When CHOP collaborates with PERK in the form of PERK-CHOP pathway, it promotes the expression of tribbles-related protein3 (TRB3), an AKT blocker [224]. Upon AKT inactivation, it represses the phosphorylation of tuberous sclerosis complex 2 (TSC2), resulting in inactivation of the mammalian target of rapamycin complex1 (mTORC1). The inactivated mTORC1 then dephosphorylates ATG13 and the ULK1/2 complex to provoke the formation of autophagosomes [225]. Moreover, the eIF2α/ATF4/CHOP pathway positively affects the expression of p62 to induce autophagic flux [226].

2.1.4. The role of PERK arm of UPR and autophagy in drug resistance and cancer cell survival

As mentioned earlier, the activated PERK phosphorylates eIF2α and NRF2 after dissociating from GRP78 [227]. Phosphorylated NRF2, in turn, activates ROS-scavenging enzymes, making cells resistant to hypoxia [228]. Hence, the inhibition of PERK enhances chemosensitivity by increasing ROS accumulation [160,229]. GSK2656157 is a well-known PERK inhibitor that blocks the phosphorylation of eIF2α and the expression of ATF4 and CHOP, following the suppression of PERK autophosphorylation. GSK2656157 also refuses angiogenesis as a pivotal process in tumor cell growth and development [230]. More interestingly, PERK-induced up-modulation of cellular inhibitors of apoptosis (i.e., cIPA1 and cIPA2) can protect cells against tunicamycin-induced death [231].

The PERK-eIF2α pathway has also been demonstrated to be up-regulated in chronic myeloid leukemia (CML) cells with high expression levels of BCR-ABL [232]. An intriguing study revealed that transfecting CML cells with dominant-negative mutants of PERK or dominant-negative eIF2α-S51A mutant, significantly increases the apoptotic pathway activity in these cells when treated with imatinib [233]. Recent findings suggested that PERK arm of UPR is involved in the crucial effects of Simva-TMZ combination therapy, enhancing cell death and improving TMZ effectiveness in GBM cells. Surprisingly, Simva-TMZ, through PERK, causes the p62 accumulation and regulates autophagy flux inhibition in U87 and U251[22] .

PERK activation has also been implicated in cervical cancer stem cells (CSCs), which exhibit resistance to ER stress-triggered apoptosis [234]. Consequently, pharmacological suppression of PERK and not IRE1 makes CSCs sensitive to ER-stress induced apoptosis. However, when these corresponding CSCs undergo cisplatin therapy, they become dependent on IRE1 rather than PERK. It can be concluded that CSCs defeat tumor progression-related stresses by triggering the PERK. Switching from PERK to IRE1 due to tolerating extra chemotherapeutic stress is actually a potential mechanism to protect cells from CHOP-induced cell death [24,234]. Consistent with these facts,

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targeting the PERK-eIF2α axis emerges as another effective approach to overcome challenges associated with cancer therapy.

2.1.5. Interplay between ATF6 and autophagy

When ATF6, a third component of the Unfolded Protein Response (UPR), detects an elevation in the levels of misfolded proteins, it exposes Golgi localization signals to ensure smooth transport to the Golgi apparatus (GA). Subsequently, Site 1 and Site 2 proteases initiate the cleavage of ATF6, resulting in its activated form[235]. This activated ATF6 then translocates to the nucleus, where it binds to elements associated with endoplasmic reticulum (ER) stress. Upon binding, ATF6 enhances the expression of essential factors involved in proper protein folding, namely GRP78, XBP1, CHOP, and PDI (protein disulfide isomerase) [236].

Atf6 has been reported to play an essential role in autophagy induction by assisting the death-associated kinase 1 (*Dapk1*) [237]. The underlying mechanism of this type of autophagy induction is an interactive connection between ATF6 and C/EBP-β to generate a transcriptional complex to promote the expression of DAPK1 through binding to CRE/ATF elements located on the DAPK1 promoter [238]. Along with this finding, silencing of *ATF6* with specific small hairpin RNAs (shRNAs) can significantly decrease the expression of *DAPK1* and subsequent formation of autophagosomes. Indeed, *DAPK1* is a major contributor to the formation of autophagosomes through phosphorylating of BECN. Upregulation of CHOP, XBP1, and GRP78 also contributes to ATF6-triggered autophagy [239]. This axis has transformed ER stress-stimulated autophagy into a more complex process.

2.1.6. The role of ATF6 arm of UPR/ autophagy in drug resistance and cancer cell survival

Although ATF6's role in cancer drug resistance is not fully understood, it has been revealed as a crucial contributor to chemoresistance. A great model has been described for ATF6-induced imatinib resistance in leukemia [240]. In this study, *PDIA5* was identified as responsible for the activation of *ATF6* and export of ER proteins in a way that *PDIA5* impairment could mitigate the expression levels of ATF6-specific target genes. In addition, the down-regulation of *ATF6* promoted chemosensitivity in imatinib-resistant leukemia cell line (K562R cells) [240]. ATF6 activation has also been demonstrated in tunicamycin or thapsigargin-treated melanoma, suggesting the essential role of ATF6 in protecting melanoma cells against ER stress-induced death [241].

Beyond its role in drug resistance and cell survival, *ATF6* has been reported to be involved in cancer recurrence [242]. The activation of *ATF6α* induced by p38 signaling has been shown in D-HEp3 cell line. More interestingly, the number of viable D-HEp3 cells with silenced *ATF6α* expression significantly decreases after doxorubicin treatment. It is noteworthy that *ATF6α* exerts its anti-chemotherapeutic effects through the activation of the mammalian target of rapamycin (mTOR) [243]. Therefore, targeting the ATF6 arm of the UPR presents another effective approach to overcome challenges associated with cancer therapy (**Figure 3**).

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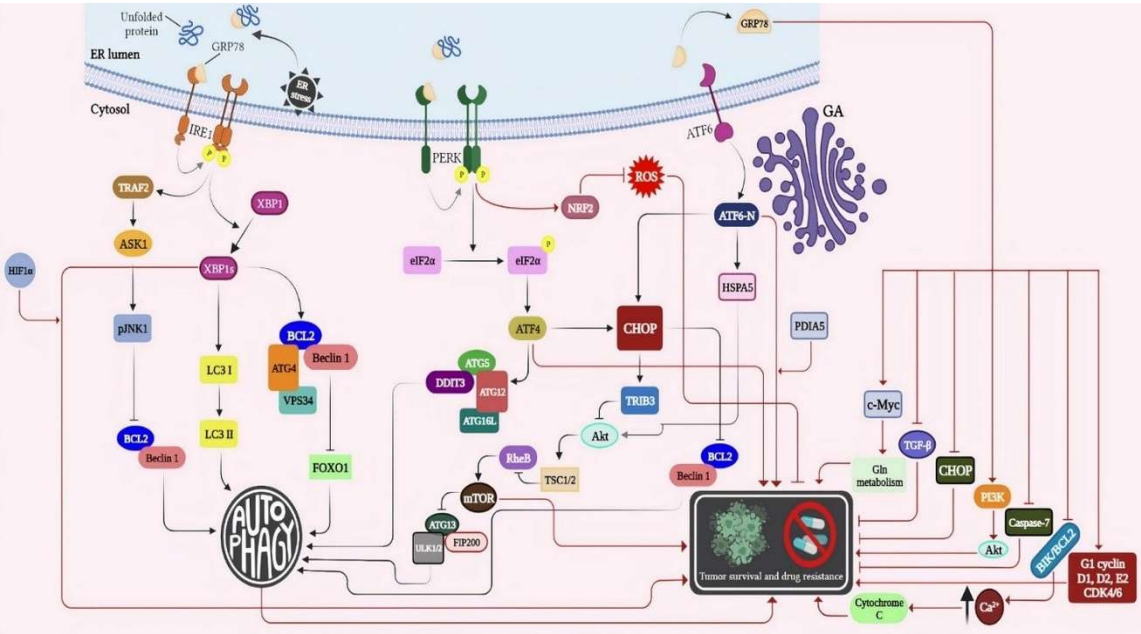

Figure 3. Schematic views of crosstalk between the UPR, autophagy, tumor survival, and drug resistance. The presence of unfolded proteins inside the ER lumen, accompanied by the ER stress, promotes the dissociation of GRP78 from IRE1 and PERK, leading to dimerization and auto-phosphorylation of these two proteins and subsequent activation of XBP1 and eIF2α, respectively. The activated XBP1 and eIF2α (i.e., XBP1s and phosphorylated eIF2α) then trigger their downstream targets to modulate autophagic flux, as well as tumor survival/drug resistance. On the other hand, ATF6, the UPR's third arm, activates ATF6-N to target autophagy and tumor survival/drug resistance. GRP78, by itself, regulates particular pathways in order to stimulate and/or suppress tumor survival and chemoresistance. Follow the arrows for more detailed information. AKT, Protein kinase B; ASK1, Apoptosis signal-regulating kinase 1; ATF6, Activating transcription factor 6; ATG, Autophagy-related protein; BCL2, B-cell lymphoma apoptosis regulator 2; BIK, BCL-2 interacting killer; Ca, Calcium; CDK, Cyclin-dependent kinase; CHOP, C/EBP homologous protein; DDIT3, DNA damage inducible transcript 3; eIF2α, Eukaryotic initiation factor-2α; ER, Endoplasmic reticulum; FIP200, Focal adhesion kinase family-interacting protein of 200 kDa; FOXO1, Forkhead box O1 ; GA, Golgi apparatus; Gln, Glutamine; GRP78, Glucose-regulated protein of 78 kDa; HIF1α, Hypoxia inducible factor 1α; HSPA5, Heat shock protein family A member 5; IRE1, Inositol-requiring enzyme 1; LC3, Light chain 3; mTOR, Mammalian target of rapamycin; NRF2, Nuclear factor-erythroid factor 2-related factor 2; p, Phosphate; PDIA5, Protein disulfide isomerase family A member 5; PERK, Protein kinase RNA-like endoplasmic reticulum kinase; PI3K, Phosphoinositide 3-kinase; pJNK1, Phosphorylated c-Jun N-terminal kinase 1; RheB, Ras homolog enriched in brain; ROS, Reactive oxygen species; TGF-β, Transforming growth factor-βeta; TRAF, Tumor necrosis factor receptor-associated factor; TRIB3, Tribbles pseudokinase 3; TSC1/2, Tuberous sclerosis complex 1/2; ULK1/2, Unc-51 like autophagy activating kinase 1/2; XBP1, X-box-binding protein 1; XBP1s, spliced XBP1.

2.1.6. Other pathways involved in ER stress-induced autophagy

Based on previous studies, proper ER function positively supports autophagic flux, which must be initiated and elongated accurately. Hence, inhibiting a ER key regulator and/or molecular chaperone, e.g., GRP78, can disrupt ER function, leading to the repression of ER stress-triggered autophagy [244,245]. In this regard, Cook et al. reported that activating AMPK and TSC2 by GRP78 could stimulate autophagy in breast cancer by suppressing the mTOR [246]. P38 MAPK signaling cascade is another central pathway to the mentioned phenomenon; the accumulation of misfolded acid α-glucosidase (GAA) can stimulate ER stress, which enhances LC3 II levels in Pompe disease. Interestingly, a significant decrease in p38 phosphorylation, achieved by employing a pharmacological chaperone for misfolded GAA and/or a particular inhibitor of p38 MAPK, can

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markedly mitigate p38-correlated ER stress [247]. SB203580 is one of these inhibitors that can suppress ER stress-triggered autophagy. It is important to highlight that the IRE1/ASK1 pathway leads to the phosphorylation of p38. Additionally, within the IRE1/ASK1 axis, JNK is a commonly targeted component, often involving TRAF2. However, it's noteworthy that no alterations in the levels of phosphorylated JNK and ERK have been documented in cells exposed to ER stress. As a result, the exact pathway among the three MAPK pathways that serves as an autophagy inducer during ER stress conditions appears to remain uncertain. [214].

ER stress promotes the translocation of misfolded proteins to the cytoplasm, where they undergo ubiquitination and subsequent removal by the by the ubiquitin-proteasome system, a process known as ER-associated degradation (ERAD) [248,249]. When the ERAD is insufficient for degradation, ER stress-induced autophagy serves as an alternative process to eliminate misfolded proteins in order to maintain proteostasis [250]. Autophagy may also neutralize ER expansion by sequestering the ER into double membrane-bounded and autophagosomal-like structures [251]. ER stress caused by hypoxia/ischemia can be reduced in vivo by the powerful autophagy activator rapamycin [169] , but it can be completely restored by the pharmacological autophagy inhibitor 3-methyladenine (3-MA).[252].

In general, chemoresistance can occur due to multiple factors such as amplified drug efflux, changes in drug targets, drug inactivation, all of which contribute to accelerating drug removal from cancerous cells. The potential role of UPR and the UPR-autophagy network in cancer drug resistance is now evident. Cancer cells typically employ the adaptive power of the UPR arms to ensure survival when exposed to chemotherapeutics. Therefore, suppressing XBP1, GRP78, ATF6, and ATF4 is believed to contribute to the re-sensitization of chemoresistant cells, suggesting that all UPR's arms and their downstream factors can be considered as potential targets to overcome drug resistance. Multiple processes, such as oxidative stress and ROS generation, occur upstream or downstream of the UPR, and they may be directly or indirectly involved in chemoresistance. Since it is crucial to understand the interplay between these up-/downstream events and UPR, the following section will provide comprehensive information in this regard.

3. NRF2 controls UPR and proteostasis

As mentioned before, ER stress resulting from the aggregation of misfolded proteins induces UPR by stimulating three signaling branches equipped with the IRE1-XBP1, PERK -eIF2a, ATF4, and ATF6 [253]. The deposition and aggregation of misfolded proteins trigger the unrestricted generation of ROS from mitochondria, ER, and other sources, which could activate NRF2 [254]. The NRF2-KEAP1-ARE pathway is a flexible cellular response that safeguards against oxidative and xenobiotic stress. ROS or electrophile-induced changes in Keap1 cysteine sites prevent NRF2 degradation, leading to its accumulation in the cytosol. NRF2 then enters the nucleus, partnering with MAF proteins to activate genes with ARE sequences in their regulatory regions. This process enhances the cell's ability to counter stress (**Figure 4A**, canonical pathway) [255].

During cellular stress, NRF2 triggers the activation of cytoprotective genes, which encode a network of enzymes collaborating to detoxify drugs through phases I, II, and III, and to eliminate pro-oxidants, maintaining cellular hemostasis. Notably, SQSTM1/p62, a protein acting as an autophagy adapter, is instrumental in orchestrating the formation of protein aggregates marked for autophagic turnover. This suggests that p62 plays a role in selectively removing protein burdens via autophagy. In SQSTM1/p62, the 349-DPSTGE-354 motif located in its KEAP1-interacting region (KIR) domain is pivotal. This motif establishes a direct interaction between p62 and KEAP1 [256]. Consequently, p62 sequesters KEAP1 within autophagosomes, hindering the ubiquitination of NRF2. As a result, the NRF2 signaling pathway becomes activated, contributing to cellular defense against stress-induced damage[255] (**Figure 4B**, noncanonical pathway).

Moreover, stress-induced PERK activity initiates the phosphorylation of NRF2, resulting in the dissociation of the NRF2/KEAP1 system and subsequent activation of NRF2 [257]. NRF2 acts as a pivotal central hub for sensing critical signals arising from the accumulation of misfolded proteins, orchestrating a coordinated transcriptional response. This function mirrors that of SKN-1, the C.

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elegans homolog of NRF2, which triggers certain aspects of UPR genes, such as XBP1 and ATF6, thereby promoting a UPR strategy to preserve endoplasmic reticulum integrity and protein homeostasis [258]. Notably, the activation of UPR target genes by SKN-1 may be mediated through NRF1[259]. Additionally, NRF2 contributes to the induction of ATF4 expression, a protein closely associated with amino acid metabolism and the ability to withstand oxidative stress [260]. NRF2 and ATF4 form a heterocomplex to activate the expression of target genes to, enabling the cell to withstand proteotoxic insults [39].

Furthermore, NRF2 binds to the promoters of genes coding proteasome maturation protein (POMP), an intermediate in proteasome assembly and activates its expression [261]. The heightened activation of NRF2 in cancers is strongly associated with increased proteasome activity and resistance to the proteasome blocker bortezomib [262]. In conclusion, NRF2 not only enhances proteasome activity but also upregulates the expression of antioxidant genes, facilitating cellular adaptation to stress. [39].

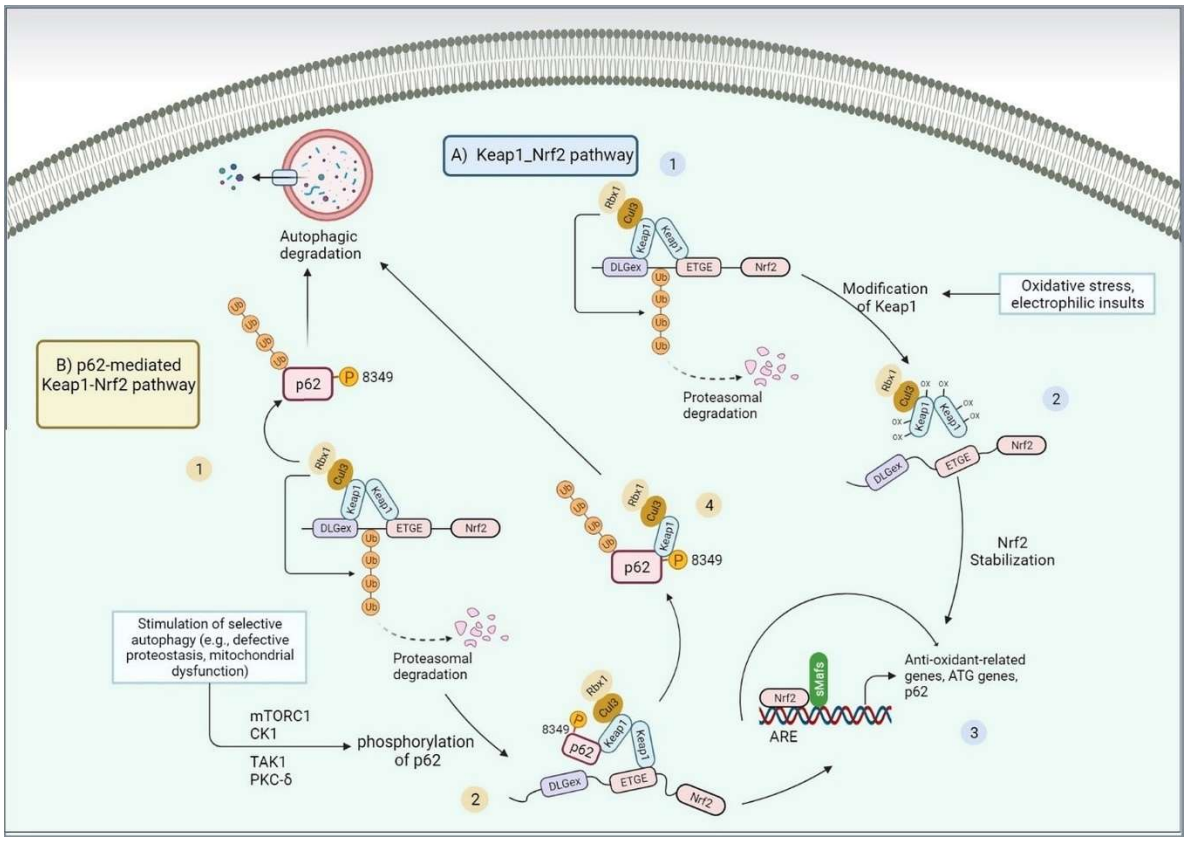

Figure 4. The KEAP1–NRF2 pathway. (A)Canonical KEAP1-NRF2 Pathway:(1) The KEAP1 homodimer functions as an adaptor protein for the Cul3-based Rbx1 ubiquitin ligase complex. It recognizes NRF2 by binding to its ETGE motif and DLGex motif, crucial for proper ubiquitination by Rbx1. Continuous ubiquitination tags NRF2 for degradation by the proteasome. (2) Oxidative stress or electrophilic exposure causes specific cysteine residues on KEAP1 to be modified by reactive oxygen species and electrophiles (OX). This results in NRF2 dissociating from KEAP1. (3) Released NRF2 translocates to the nucleus, collaborating with transcription factors sMAFs, to activate target genes. (B) P62-Mediated KEAP1-NRF2 Pathway: (1) Similar to the canonical pathway, the KEAP1-Cul3-Rbx1 complex interacts with and ubiquitinates NRF2, leading to its proteasomal degradation. P62, too, is targeted for autophagic degradation through its ubiquitination by the ubiquitin ligase. (2) Selective autophagy triggers P62-mediated pathway in response to factors like defective proteostasis, mitochondrial dysfunction, and invasive microbes. Phosphorylation of P62's Ser349 by mTORC1, CK1 (CSNK1A1), TAK1, and PKCδ hampers KEAP1-DLGex motif interaction, preventing new NRF2 from binding to KEAP1. (3) Stabilized NRF2 translocates to the nucleus, inducing the transcription of its target genes, including P62. (4) P62's ubiquitination on lysine 420 by KEAP1-Cul3-Rbx1 complex

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augments its autophagic degradation, whether bound to KEAP1 or not. ARE, antioxidant response element.

3.1. NRF2 modulates autophagy

Autophagy relies on a coordinated collaboration among a group of proteins that collectively assemble autophagosomes and autolysosomes [263,264]. Additionally, selective cargo-recognizing proteins identify specific targets and guide them toward degradation[265,266]. Nrf2 contributes to the upregulation of mRNA levels for autophagy-related genes like *Sqstm1/p62*, calcium-binding and coiled-coil domain-containing protein 2 (*Calcoco2/Ndp52*), unc-51-like kinase 1 (*Ulk1*), autophagy protein 5 (*Atg5*), and gamma-aminobutyric acid receptor-associated protein-like 1 (*Gabarapl-1*). These genes collectively contribute to facilitating the autophagy process [267]. Surprisingly, in conditions induced by NRF2, a therapeutic focus on promoting autophagy might prove ineffective. Paradoxically, insufficient autophagy results in the accumulation of oxidized proteins or organelles, triggering NRF2 activation. Notably, a deficiency in autophagy results in the buildup of p62, a multifunctional cargo receptor that can sequester KEAP1 and stabilize NRF2, ultimately leading to NRF2 induction [268]. Hence, a reciprocal loop is formed between p62 and NRF2, establishing a positive feedback mechanism that governs a multitude of cellular processes. [39,265].

The function of autophagy in cancer is slightly paradoxical; it can contribute to eliminating tumor cells in some instances, while in others, cancer cells may suppress autophagy as a defense against nutrient deficiency, oxidative stress, and other stressors [269-272]. Autophagy defects can potentially promote cancer through Nrf2 induction. In a study, the inhibition of the critical autophagy gene *Atg7* in the liver of mice induced accretion of p62, Nrf2 stimulation, and the development of hepatocellular carcinoma (HCC) [273]. In addition, ectopic expression of p62 was sufficient to activate NRF2 and promote development of HCC [265], highlighting the fundamental role for p62 elevation in HCC generation downstream of autophagy deficit. In pancreatic ductal adenocarcinoma, perturbation of inflammation- induced autophagy also triggered p62-mediated stimulation of NRF2, contributing to neoplasm progression through NRF2-intervened MDM2 induction [274].

In cancers, not only NRF2 stimulation through p62 is pro-tumorigenic, but it also performs a vital role in the cellular response to autophagy defects in normal cells. NRF2 preserves small intestine damage and animal death after entire body deletion of ATG7 and TP53 [20], implying that NRF2 induction by p62 is crucial for cellular adaptation and homeostatic management. NRF2 may regulate the expression of specific proteasome subunits, which could clarify why it is protective in the background of autophagy deficiency [265]. Furthermore, in response to proteasome defects, NRF2 is also activated and subsequently collaborates with autophagy to respond to the stress[275]. In summary, these studies emphasize the critical role for NRF2 in responding to autophagic defect and/or proteasomal strain [265]. Unresolved ER stress can trigger programmed cell death, but certain tumor cells evade ER stress signaling to promote their growth, and NRF2 activation plays a role in this evasion[276]. For instance, the PERK enzyme inhibits cap-dependent translation to alleviate proteotoxic stress while promoting ATF4 expression[277]. ATF4 is associated with resistance against oxidative stress, enhanced amino acid metabolism, and autophagy induction, possibly through interaction with NRF2. NRF2 and ATF4 mutually induce each other's expression, forming a positive feedback loop[253] . NRF2 and ATF4 prevent ER stress-induced cell death, enabling cancer cells to endure proteotoxic stress. Furthermore, unresolved ER stress triggers the UPR and activates the ER-associated degradation (ERAD) pathway. NRF2-induced proteasome genes aid in ERAD, thus reducing proteotoxic stress [253,257].

4. Evidence show overexpression of NRF2 promotes post-initiation stages of cancer

Although the overexpression of NRF2 is not sufficient to launch tumorigenesis, its upregulation has been established in certain types of cancers. NRF2 overexpression contributes to carcinogenesis by amending oxidative stress and promoting cell growth in different ways, such as over activation of pentose phosphate pathway (PPP), serine synthesis, autophagy, and weakening the immune system [76]. In a murine Kras oncogenic pancreatic cancer model, research about the suppressive action of

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oxidative stress on carcinogenesis has demonstrated that Nrf2 is needed for Kras-guided pre-invasive pancreatic intraepithelial neoplastic lesions. Likewise, through a CRISPR-Cas9 approach, deletion of *Keap1* has been shown to hasten Kras-guided lung adenocarcinoma [76,278]. Since cancer cells generate higher levels of ROS to sustain growth and must tolerate oxidative stress within metastasis, it is highly possible that overexpression of NRF2 gives advantages to the tumor, so the subsequent upregulation of antioxidant genes inhibits ROS-induced cell apoptosis [279]. In addition to the increased activity of antioxidant enzymes that eliminate ROS, NRF2 also handles the transcription of PPP genes in both the oxidative and non-oxidative arms. The overexpression of this pathway could contribute to the existence and proliferation of cancer cells by enhancing the production of NADPH and ribonucleotides [280].

In addition to the elevation of antioxidant enzymes regulated by NRF2, there are alternative strategies available to boost glutathione (GSH) levels during advanced cancer stages. One effective approach involves increasing the production of NADPH through the folate pathway. Other techniques encompass activating mTOR signaling, raising mitochondrial metabolism, and facilitating glutamine flux through estrogen-related receptor α (ERRα) pathways [281]. Furthermore, the indirect influence of NRF2 over ATF4 governs serine synthesis by controlling the transcription of genes encoding phosphoglycerate dehydrogenase (PHGDH), phosphoserine aminotransferase-1 (PSAT1), and serine hydroxymethyltransferase-2 (SHMT2). While serine serves as a vital intermediate for glutathione and nucleotide synthesis, excessive activation of NRF2 can stimulate cancer cell growth [260]. In conjunction with antioxidant systems and the pentose phosphate pathway (PPP), NRF2 also impacts the transcription of proteasome subunits and components within the autophagy complex. The hyperexpression of NRF2 activates this system, potentially providing support for cancer cell viability and growth [76]. Notably, autophagy plays a crucial role in suppressing liver carcinogenesis by preventing the buildup of defective mitochondria and mitigating oxidative stress. This is exemplified through studies involving mice with mosaic deletion of *Atg5* and hepatocyte-specific deletion of *Atg7*, where hepatic adenomas developed [282]. However, before tumor stabilization occurs, autophagy typically stimulates cancer cell proliferation by recycling unnecessary cellular components to fuel oxidative phosphorylation, thus enabling these cells to overcome nutrient stress [76].

Hence, the role of autophagy in cancer is context-dependent and might be linked to the timing of NRF2 stimulation via an unconventional mechanism [253]. Autophagic flux intensifies in response to oxidative, proteotoxic, and metabolic stresses, aiming to restore homeostasis and impede genome instability, inflammation, and overall tissue damage [283]. Notably, regulated and effective autophagy in normal cells or tissues acts to suppress the initiation of cancer [253]. However, many cancer cells rely on autophagy to withstand heightened levels of proteotoxic, metabolic, oxidative, and hypoxic stress. Notably, cancers carrying *KRAS* mutations heavily depend on extensive autophagy for proliferation and invasion [253,284]. Disrupting autophagy in NSCLC through the activation of $Kras^{G12D}$ and $Braf^{V600E}$, either alone or combined with Trp53 deletion, halts cancer progression and leads to less severe damages[285]. That is why autophagy inhibitors are utilized in cancer treatment [253,286].

Yet, in cases where these agents fail to effectively initiate cellular death, they may inadvertently trigger NRF2 via non-canonical pathways, resulting in chemo-resistance and prolonged cell survival. Moreover, given NRF2's role in governing the transcription of autophagy-related genes like *Sqstm1/p62*, Calcoco2, *Ulk1*, *Atg5*, and *Gabarapl1*, non-canonical activation of NRF2 could undermine the effectiveness of treatments targeting autophagy [253,267]. Nonetheless, a combined therapeutic strategy addressing both autophagy and Nrf2 could potentially overcome this resistance. On the other hand, impaired autophagy, achieved through genetic disruption of components like ATG5, ATG7, or BECN1, has been shown to trigger liver cancer [282]. The impairment of autophagy (via deletion of *ATG5*, *ATG7*, or *BECN1*) leads to an accumulation of SQSTM1/p62, resulting in subsequent non-canonical sustained activation of NRF2 [253]. Interestingly, studies have illustrated that the elimination of *Sqstm1/p62* reinstates the carcinogenicity linked to malfunctioning autophagy in mice, which corresponds to a reduction in Nrf2 levels [282]. Correspondingly, *Nrf2* deletion

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inverses the impacts of malfunctioned autophagy made by deletion of Atg5 in mouse liver and lessens carcinogenesis [77,253].

4.1. NRF2 as double-edged sword in cancers

Cancer chemopreventive agents serve to safeguard normal tissues from the initiation of carcinogenesis by activating NRF2-targeted genes. These genes encode enzymes that mitigate the genotoxic and cytotoxic effects of carcinogens. However, extended activation of NRF2 in cancer cells can predictably result in resistance to both drug and radiotherapy treatments. Thus, NRF2 demonstrates a dual nature, acting as a "double-edged sword" by facilitating both cancer chemoprevention and the promotion or progression of tumors [76]. The potential adverse consequences arising from the overstimulation of NRF2 in pre-neoplastic lesions and cancer cells have been termed the "dark side" of this transcription factor by Donna Zhang's research group [287]. This aspect is underscored by clinical observations linking elevated NRF2 expression to unfavorable prognosis and decreased overall survival rates among patients with lung, head and neck, esophageal, gastric, liver, and colorectal cancers. [76].

Tumor cells are theoretically more sensitive to oxidative stress than normal cells due to their high levels of ROS induced by activation of oncogenes. Therefore, therapeutic approaches aiming to increase ROS production or decrease their antioxidant capacity have been considered as a means of generating selective toxicity in cancers [288].

4.2. Targeting of Nrf2 Signaling to fight Chemo-resistance: NRF2 inhibitors

Regarding the distinct NRF2 levels between cancer and normal cells, inhibiting NRF2 activity with small molecular inhibitors might be a safe and promising strategy to overcome multidrug resistance in cancers. For example, sequential therapy of breast cancer cells with vitamin C and quercetin has been found to reduce the expression of NRF2 at both the mRNA and protein levels [289]. Additionally, combination therapy with vitamin C and quercetin has been reported to enhance the cytotoxic feature of chemotherapeutic drugs in breast cancer cells as compared with the drug treatment alone [290].Developing novel and potent NRF2 inhibitors is undoubtedly a challenging task, although only a small number of NRF2 inhibitors have been proposed for further preclinical experiments. [291].

There is a large number of synthetic molecules and flavonoids that inhibit Nrf2, but in this review, we only focused on NRF2 inhibitors studied based on data from various preclinical and experimental models. Studies have frequently pointed to the inhibition of the NRFrf2 pathway as a promising therapeutic choice for the treatment of cancer, which requires more investigation and authentication in the clinical settings. The inhibitors we have discussed, as outlined in (Table 2), exhibit a range of inhibitory mechanisms. These mechanisms include the inhibition of overall protein synthesis (brusatol, halofuginone, camptothecin/CPT), disruption of NRF2 nuclear translocation (trigonelline, ATRA), inhibition of DNA binding (ML385), suppression of associated kinase pathways (clobetasol propionate, flavonoids), initiation of NRF2 degradation (clobetasol propionate), or an effect that remains undisclosed (triptolide, IM3829, AEM1).

The use of this approach is exemplified by well-known instances such as the quassinoid brusatol [292], as well as other compounds like retinoic acid [261] and natural flavonoids such as luteolin, apigenin, chrysin, and wogonin [293-296]. Brusatol, derived from the natural product of Brucea javanica, functions as an NRF2 inhibitor, validated through a stable ARE-luciferase reporter gene cell line known as MDA-MB-231-ARE-Luc [228]. Recent studies have shown that it effectively reduces NRF2 protein levels across various cell lines, including MDA-MB-231, Hela, Ishikawa, and SPEC-2, while *NRF2* mRNA levels remain unaffected. Furthermore, brusatol does not impact *KEAP1* protein and mRNA levels. Notably, it sensitizes A549 cells and xenografts to a range of chemotherapeutic drugs including carboplatin, 5-fluorouracil, etoposide, and paclitaxel [292]. Histological investigation showed that brusatol treatment decreased the expression of antioxidant genes such as NRF2, solute carrier 7A11 (SLC7A11), GCLC, and GCLM in a xenografted glioma model [297].

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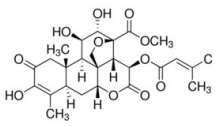
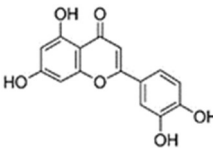
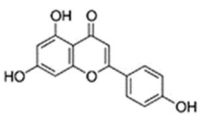
Table 2. Research Summary on Nrf2-ARE Inhibitors in Preclinical and Experimental Models.

Classification and origins	Compound	Structure	Dose and time	Mechanism	Model and effect	Refs.
Brucea javanica Plant	Brusatol (Bru)		2 mg/kg, five times for 16 days via intraperitoneally	↓ NRF2/GSH axis	↓tumor mass ↓NRF2, SLC7A11, GCLC, and GCLM expression Six-to-eight-week-old NSG mice	[298]
Flavonoid	Luteolin (Lut)		40 mg/kg BW/day; 14 days	Unclear	↓NRF2 protein levels in mouse liver and intestine (C57BL/6, Male, 6 weak old)	[293]
Flavonoid	Apigenin (Api)		In vivo: 50 mg/kg BW/day; every 3 days for 7 times	PI3K/Akt pathway: ↓p-Akt	↓tumor size in male BALB/c nude mice (aged 5 weeks) that were implanted with BEL-7402 cells; ↓level of NRF2 protein	[294]

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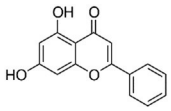
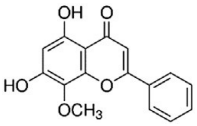
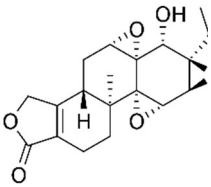
					↓Tumor size of mice	
Flavonoid	Chrysin (Chry)		40 and 80 mg/kg/day by oral gavage; once a day, 5 times per week	↓ERK/NRF2 signaling pathway	(male BALB/c athymic nude mice, 4–6 weeks) ↓translocation of NRF2 into the nucleus and ↓ expression of (HO-1) and NQO-1	[295]
					NOD/SCID immunodeficient mice (aged 5–6 weeks)	
Flavonoid	Wogonin (Wog)		40 mg/kg intravenously, once every other day for 30 days	↓NF-κB/NRF2 pathway	↓ nuclear NF-κB p65, p-Stat3 and NRF2 expression and ↓phosphorylation of IKKα and IκBα ↓NF-κB p65 and NRF2 expression in spleen	[296]
A traditional Chinese medicine	triptolide		0.25 mg/kg, by intraperitoneal every other day for 10 days	transcriptional regulation of NRF2	↓Tumor growth and weight C57BL/6 mice (6–8	[299]

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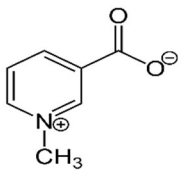
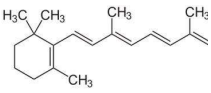
					weeks, male) ↓NRF2 and downstream genes Gclc and Gclm increases the chemosensitivity of xenograft tumors to epirubicin	
An alkaloid	Trigonelline (Trig)		0.02 mg/kg intraperitoneally for 21 days	↓ a nuclear level of activated NRF2 protein	↓tumor growth and weight 8-week-old female SCID–beige mice ↑responsiveness of various cell lines to both anticancer drugs and apoptosis induced by TRAIL.	[300]
Vitamin derivative	all-trans-retinoic acid		10 μM, 48h 40 mg/kg, three times weekly via intraperitoneally	↓NRF2/POMP axis	↓cell viability, purified CD138+ plasma cells from patients	[261]

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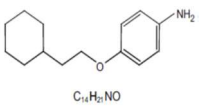
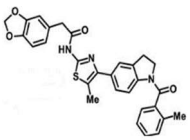
					with myeloma ↓tumor growth 6-week-old non-obese diabetic/severe combined immunodeficiency (NOD/SCID) mice	
Aniline-based compound	IM3829 (4-(2-Cyclohex-ylethoxy) aniline)		5mg/kg/day), intraperitoneally for 4 days	↓NRF2-binding activity and expression of NRF2 target genes, increase ROS accumulation in irradiated cell	↓tumor growth, without changes in body weight, Five-week, female, athymic BALB/c nude mice	[301]
A probe molecule that binds to Nrf2	ML385		30 mg/kg daily Monday to Friday), intraperitoneally for 3 weeks	blocks NRF2 transcriptional activity	↓tumor growth, athymic nude mice, ↓NRF2, NQO1, and ABCG2 expression	[302]

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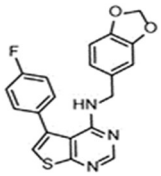
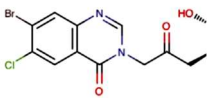
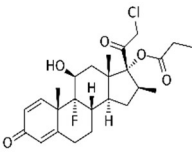
A chemical substance	ARE expression modulator 1 (AEM1)		50 mg/kg, BW; twice a day for 10 days	Unclear	↓Tumor growth of mice which were implanted with A549 cells (Nude mice, Male, 6 wk old)	[303]
A febrifugine derivatives	halofuginone		0.25 mg/kg, every day intraperitoneally	Inducing a cellular amino acid starvation response that repressed protein level of NRF2	↓tumor growth, 6–8-week-old male nude mice, enhances the anticancer effects of cisplatin. without severe toxicity	[304]
Corticosteroid drug	Clobetasol propionate		CP (0.5 or 1 mg/kg, n = 5 per group) were intraperitoneally injected every 2 days (3 days per week) for 40 days.	↓NRF2 in a GR and GSK3-dependent manner	Balb/c-nu mice (6–8 weeks). ↓NRF2 and the expression of its key targets in KEAP1 mutant NSCLCs and induction of oxidative stress. ↓tumor growth	[305]

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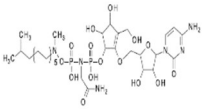
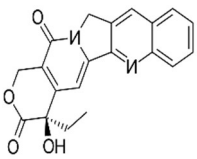
					and shrinkage of tumor size	
Purified from Streptomyces sp. 3728-17 strain	K-563		100 mg/kg, subcutaneously to the mice twice a day for 1 day	↓Keap1/ NRF2 pathway	Male severe combined immunodeficient (SCID) mice, 5 weeks' old ↓expressions of Keap1/NRF2 pathway Targeted genes (HMOX1, GCLC, GCLM,AKR1C1, ME1, NQO1, and TXNRD1)	[306]
Anti-tumor drug	Camptothecin		CPT (3 mg/ kg body weight) were intraperitoneally (IP) injected twice a week for a total of three times.	↓NRF2–ARE pathway activity	↓tumor growth BALB/Cnu/nu mice (4–6 weeks, male). Sensitization of a variety of cancer cells and a xenograft hepatocellular carcinoma model to chemothera	[307]

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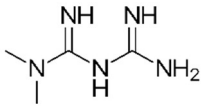
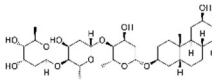
					peutic drugs	
Type 2 diabetes drug	Metformin		200 µg/mL, diluted in drinking water and administered for day 22	↓NRF2, HO-1, KI-67 and PCNA expression	↓tumor growth, Female BALB/C nude mice (6-8 weeks of age) enhancing the anti-cancer effect of EGCG on NSCLC xenografts	[308]
Cardiac glycoside drug	Digoxin		0.1 mg/kg, daily, i.g for 24 days	↓Activity of NRF2 through suppressing PI3k/Akt signaling pathway	↓tumor growth In female BALB/c nude mice (aged 6 weeks, weighing 18 ± 2 g), the resistance to gemcitabine was effectively reversed by inhibiting NRF2 in SW1990/Gem and Pac-1/Gem cells.	[30]

These compounds possess drawbacks like lack of specificity and potential off-target effects. For instance, brusatol exhibits a global protein translation suppression effect [228]. Luteolin (3′,4′,5′,7-tetrahydroxyflavone) reduces both NRF2 mRNA and protein levels in A549 cells by promoting NRF2 mRNA degradation, sensitizing them to antitumor drugs. In mice, luteolin treatment decreases NRF2 protein levels and reduces tumor size in the liver and intestine [293]. Apigenin (4′, 5, 7-trihydroxyflavone) and chrysin (5, 7-dihydroxyflavone) also decrease NRF2 mRNA and protein levels, rendering hepatocellular carcinoma BEL-7402 cells more responsive to the anti-tumor drug

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doxorubicin. Recent research highlights that apigenin and chrysin's NRF2-suppressive effects stem from inhibiting the PI3K/AKT pathway. Notably, apigenin treatment induces tumor size reduction in mice implanted with hepatocellular carcinoma cells. [294].

Notably, apigenin and chrysin exhibit direct inhibition of the PI3K/AKT pathway, a critical regulator of cancer cell proliferation [228,294]. Their distinct actions on cancer cells compared to normal cells, along with their low toxicity, make them promising candidates for cancer treatment. Another compound, wogonin (5, 7-dihydroxy-8-methoxyflavone), derived from the traditional Chinese herb Scutellariae radix, has emerged as an NRF2 inhibitor methoxyflavone) [228]. Wogonin effectively counteracts drug resistance in various cell lines, including human breast adenocarcinoma MCF-7/DOX, human myelogenous leukemia K562/A02, and HepG2 cells by suppressing NRF2 mRNA and protein expression. Notably, it enhances the anticancer effects of Adriamycin in leukemia by inhibiting pY705-Stat3 and NRF2 signaling pathways[296].

Triptolide, an agent from traditional Chinese medicine, has been proven to effectively inhibit the expression and transcriptional activity of NRF2 in various cancer cell types, including non-small cell lung cancer (NSCLC) and liver cancer cells. This suppression of NRF2 activity leads to enhanced chemosensitivity of cancer cells to antitumor drugs both in laboratory settings and in a xenograft tumor model of lung carcinoma cells. [299].

Trigonelline, an alkaloid found in various plants and coffee, has the potential to enhance cell susceptibility to apoptosis by inhibiting the nuclear translocation of NRF2. This action is accompanied by a reduction in proteasomal gene expression and proteasome activity[228]. The favorable safety profile of this natural coffee constituent in both regular consumption and therapeutic applications suggests its viability for combination therapy in pancreatic and other types of cancers.[300]. All-trans-retinoic acid (ATRA), also identified as tretinoin, is a vitamin in the retinoid family of medicines [228]. As an NRF2 inhibitor, ATRA diminishes cellular levels of NRF2 and boosts the anti-prolife\rative and pro-apoptotic actions of bortezomib in resistant cells while reducing proteasome activity. The combination therapy with all-trans-retinoic acid plus bortezomib exhibited great activity versus primary patient samples and in a mice-bearing bortezomib-resistant myeloma model [261]. A number of research teams have purified several chemical libraries for small molecules that hinder NRF2 activity with various cell-dependent reporter analyses [228]. Employing ARE-directed luciferase assays, researchers found compounds such as 4-(2-cyclohexylethoxy) aniline (IM3829) [301], ML385 [302], halofuginone [304], and clobetasol propionate [305] were powerful suppressors of NRF2 activity.

IM3829 stands as the first synthetic NRF2 inhibitor, as revealed by Song et al. Their pursuit involved screening a synthetic compound library of 8000 substances through a HEK293 cell-based ARE-luciferase reporter assay, leading them to identify IM3829 [4-(2-cyclohexylethoxy) aniline] as a small-molecule NRF2 blocker [228]. This compound was found to decrease the mRNA levels of NRF2 and its target genes, HO-1 and NQO1, in both H1229 and A549 cells. In tandem with irradiation (IR) therapy, IM3829 inhibited the nuclear translocation of NRF2, increased ROS levels in lung cancer cells, and significantly delayed tumor growth in H1299 and A549 xenograft models, surpassing the effects of IR-only treatment or Dimethyl sulfoxide (DMSO). Overall, IM3829 holds potential as a radiosensitizer for non-small cell lung cancer (NSCLC) [301]. Moving on, ML385 selectively suppresses the growth of KEAP1-mutated NSCLC A549 and H460 cells while leaving normal lung epithelial BEAS2B cells, possessing wild-type NRF2 and KEAP1, unaffected. Additionally, ML385 enhances the sensitivity of NSCLC cells to the chemotherapeutic drug carboplatin both in vitro and in vivo. [302].

In a recent study, a compound called ARE expression modulator 1 (AEM1) has been identified as a potent suppressor of antioxidant response element (ARE) activity. It effectively reduces ARE-luciferase activity in 3T3 cells and downregulates HO-1 expression in A549 cells with an IC50 of 650 nM. AEM1 also enhances the susceptibility of A549 cells to the cytotoxic effects of chemotherapy drugs like etoposide, 5-fluorouracil, and doxorubicin. In vivo experiments have shown that AEM1 can inhibit tumor growth in an A549 xenograft-model. [303].

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Halofuginone, derived from febrifugine and known for its low toxicity, has been employed as an animal antibiotic [309]. It also demonstrates a dose-dependent repression of NRF2 function and enhances the effectiveness of cisplatin in fighting cancer in vivo. Similar to brusatol, halofuginone blocks NRF2's protein translation [304]. Another instance is clobetasol propionate (CP), which notably reduces NRF2 activity to 40% at a concentration of 1 nM. Treating of KEAP1 mutant cells (H2228 and A549) with CP results in decreased NRF2 target gene expression and increased accumulation of reactive oxygen species (ROS). Furthermore, the combination of CP and rapamycin has been observed to effectively hinder the growth of KEAP1-mutated tumors both in vitro and in vivo [305].

Another study investigated a newly discovered inhibitor of the KEAP1/NRF2 pathway, K563, obtained from Streptomyces sp [228]. K563 was found to hinder the expression of downstream genes and proteins related to this pathway, leading to reduced glutathione production and increased reactive oxygen species in A549 cells. It also exhibited similar effects in cancer cells with mutated KEAP1 or NRF2 genes. In vivo experiments on xenograft mice with A549 cells showed that K563 effectively suppressed the KEAP1/NRF2 signaling pathway within lung cancer tumors. [306].

CPT, known for its role as a topoisomerase inhibitor in the treatment of gastrointestinal and head and neck cancers, has also emerged as a potential NRF2 inhibitor for anticancer purposes. Chen and colleagues introduced CPT as a novel compound that can block NRF2 activity. Through this action, CPT sensitized a range of cancer cells (HepG2, SMMC-7721, A549) and even a xenograft model of hepatocellular carcinoma to various chemotherapeutic agents like As2O3, epirubicin, fluorouracil, and cisplatin. The inhibition of NRF2 by CPT specifically contributed to enhanced chemosensitivity in HepG2, A549, and SMMC-7721 cells[307].

Metformin, a traditional medication for diabetes management, has been found to impede the advancement of cancer. It inhibits the expression of HO-1 and amplifies the anticancer effects of EGCG by augmenting levels of reactive oxygen species. In a particular investigation, the size of transplanted tumors subjected to the combined treatment of metformin and EGCG exhibited reduction in comparison to the control groups. Metformin heightens the susceptibility of non-small cell lung cancer (NSCLC) cells to EGCG treatment by obstructing the NRF2/HO-1 signaling pathway. [308].

In an experimental study, the potent cardiac glucoside digoxin was found to effectively counteract drug resistance to gemcitabine in SW1990/Gem and Pac-1/Gem cells by inhibiting NRF2. Digoxin achieved this by blocking NRF2 through the suppression of the PI3K/AKT signaling pathway[30]. Given NRF2's pivotal role in cancer hallmarks, targeting this transcription factor appears to be a promising therapeutic strategy. While NRF2 activators could potentially prevent chemical carcinogenesis, inhibiting NRF2 holds promise for cancer treatment. Despite challenges in developing safe, potent, and specific NRF2 inhibitors due to NRF2's dual nature, extensive efforts have been dedicated to this area with limited success thus far. It is anticipated that upcoming years will clarify NRF2's potential as both a prognostic biomarker and a therapeutic target within cancer therapy.

4.3. Clinical Overview

Studies have indicated that inducing the NRF2 signaling pathway is a potent approach for tumor suppression and a viable strategy in anticancer therapy[87,88]. The transcription factor NRF2 plays a pivotal role in maintaining cellular redox and hemostasis, as well as in proliferation, differentiation, and the regulation of inflammation through its influence on a wide array of target genes [310-312]. Therefore, it emerges as a promising target for clinical interventions where such pathways contribute to the underlying pathophysiology. Over the past few decades, ongoing efforts have been dedicated to targeting NRF2 signaling as a therapeutic strategy. Numerous preclinical studies have investigated the targeting NRF2 pathways in diseases where inflammatory and oxidative processes constitute critical components, like autoimmune diseases. Particularly, four main NRF2 inducers are of particular interest: dimethyl fumarate, bardoxolone methyl, oltipraz and sulforaphane. These agents disruptNRF2 signaling through KEAP1, a key cytoplasmic receptor for NRF2 [312,313]. However,

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use of such agents in cancer treatment remains a topic of controversy, as knocking down NRF2 may increase susceptibility to carcinogenesis [314]. Although, NRF2 overexpression has been observed in numerous tumors, particularly in advanced stages, helping tumors in adapting to their microenvironment and inducing resistance to therapeutic strategies [315,316].

Therefore, their application in clinical setting for cancer is still in its early stages. Various compounds, such as glucocorticoid agonists [305,317] and retinoic acid receptor-alpha, which inhibit NRF2 activity [318,319] may exert NRF2-blocking activities, although they lack specificity.. However, certain compounds, such as ML385 have been identified through in silico studies, exhibiting a degree of specific interactions with NRF2 activities. ML385 inhibits the transcriptional function of NRF2 by interacting with its DNA binding domain, thereby increasing chemosensitivity of KEAP1-deficient cells [320]. AEM1 is another compound that downregulate NRF2-conrolled genes and increase chemosensitivity[303]. Additionally, a compound named 4f, a pyrazolyl hydroxamic acid, has demonstrated inhibitory effects on NRF2 activities. It increases apoptosis and reduces proliferation in acute myeloid leukemia cells [321]. A novel aziridonin, YD0514, derived from medical herb Rabdosia rubescens, targets the NRF2/ Ras homolog family member A (RHOA)/Rho-associated protein kinase (ROCK) pathway to suppress metastatic growth of breast cancer in vitro and in vivo[322]. The main component of coffee, Trigonelline, has been introduced as a potential treatment candidate for lung adenocarcinoma. It targets multiple pathways, including NRF2, cyclin D1, Nuclear Factor Kappa B (NF-κB), and BAX/Bcl2, inducing cell cycle arrest and apoptosis [323]. An alkaloid of black pepper, piperine, is another compound that suppresses NF-kB by inducing NRF-2 and has therefore found to be effective for prophylactic treatment of colorectal cancer in vivo[324].

Available evidence indicated that phytochemical antioxidants such as sulforaphane and curcumin target the NRF2/NF-kB and Androgen Receptor pathways, making them proper candidates for chemoprevention in prostate cancer[325]. As a polyphenolic composition of soy-based plants, daidzein modulates immune responses and antioxidant function in mice with Benzo(a)pyrene -Induced Lung Cancer by targeting Proliferating Cell Nuclear Antigen (PCNA)/ NF-κB, Cytochrome P450 Family 1 Subfamily A Member 1 (CYP1A1), and NRF[326]. Another in vitro and vivo study indicated that downregulation of NRF2/Heme oxygenase (HO-1) by miR-144-3p increased the anticancer effect of curcumin in non-small cell lung cancer (NSCLC)[327]. It has also been shown that L-carnosine reduces the peripheral neuropathy induced by oxaliplatin in colorectal cancer patients by targeting Nrf-2/ NF-κB pathways[328]. Taken together, NRF2 may be considered as a promising signaling target for cancer treatment. Further studies will contribute to identifying the exact clinical effect of NRF2 in cancer therapy. Understanding the intricate connections between NRF1, NRF2, redox homeostasis, PERK, autophagy, and chemo sensitivity opens doors to novel therapeutic interventions. Targeting specific components of these pathways could enhance the efficacy of chemotherapy in a patient-tailored manner. Developing biomarkers to assess NRF1/NRF2 activity, redox status, and autophagy levels could guide treatment decisions, optimizing outcomes in diverse cancer contexts.

5. Conclusion

NRF2 plays a crucial role in the hallmarks of cancer, acting as a double-edged sword in both the promotion and prevention of different tumors. Activation of UPR and autophagy by NRF2 may result in cancer cell survival and chemoresistance or cancer cell death during the progression of malignancies, depending on the stage and cellular origin. Therefore, proper targeting of Nrf2 may be a promising strategy in overcoming chemoresistance,a major obstacle in cancer therapy. Nrf2-targeting agents can be employed to tackle chemo-resistance in a variety of cancers. The crosstalk between ER-stress, UPR, autophagy, and NRF2 signaling pathways has recently received considerable attention. the use of antioxidant supplements and activation of the NRF/KEAP1 pathways in individuals undergoing chemotherapy are topics of controversy. Adjusting the internal levels of antioxidants, which hold therapeutic promise , poses a dual challenge. While these agents have the potential to diminish the effectiveness of chemotherapy by eliminating reactive oxygen species (ROS), they can also contribute to the toxicity induced by chemotherapy. These conflicting

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outcomes suggest that the impact of supplementing antioxidants during chemotherapy varies based on the specific cellular environment of the tumor. Consequently, achieving an optimal balance between the cancer-preventive and cancer-promoting functions of NRF2 may offer clinical benefits to cancer patients.

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Abbreviations

3-MA	3-Methyladenine
5-FU	5-Fluorouracil
ABC	Advanced Breast Cancer
ABCCs	Multidrug resistance (MDR)-associated proteins
ABCG2	Breast cancer resistance protein
AEM	Are Expression Modulator
AKRs	Aldo-Keto Reductases
AKT	Protein kinase B
ALDH1	Aldehyde Dehydrogenase 1
AMPK	Adenosine monophosphate-activated protein kinase
AP-1	Activator protein 1
ARE	Antioxidant Response Element
ARS	Antioxidants and redox signaling
ASK1	Apoptosis-signal regulating kinase 1
ATF	Activating Transcription Factor
ATG	Autophagy-related protein
ATRA	All-Trans-Retinoic Acid
BACH1	BTB and CNC homology 1
BCRP/ABCG2	Breast cancer resistance protein
BECN	Encoding beclin
BRAF	B-Raf proto-oncogene
BRG-1	Brahma-Related Gene 1
bZIP	Basic Region/Leucine Zipper
CALCOCO2	Calcium-Binding and Coiled-Coil Domain-Containing Protein 2

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CBP cAMP -binding protein
CBRs Carbonyl Reductases
CDDP Cisplatin
CHD6 Chromodomain Helicase Dna-Binding Protein 6
CHOP Homologous protein
cIPA Cellular inhibitors of apoptosis
CML Chronic Myeloid Leukemia
CNC Cap 'N' Collar
CNC-bZIP Collar Basic Region Leucine Zipper
COX-2 Cyclooxygenase-2
CP Clobetasol Propionate
CPT Camptothecin
CQ Chloroquine
CREB cAMP-response element binding protein
CSCs Cancer Steam Cells
CTX Cytotoxic Chemotherapy
CYPs Cytochrome P450s
DAPK1 Death-Associated Kinase 1
DMSO Dimethyl sulfoxide
EBP Enhancer Binding Protein
EGCG Epigallocatechin-3-gallate
eIF2a Initiation Factor 2-Alpha
EMT Epithelial-Mesenchymal Transition
ER Endoplasmic Reticulum
ERAD ER-associated degradation
ERRα Estrogen-Related Receptor A
FOXO-1 Anti-apoptotic forkhead box O-1
G6PD Glucose 6-phosphate dehydrogenase
GA Golgi apparatus
GAA Acid α-glucosidase
GABARAPL1Gamma-aminobutyric acid receptor-associated protein-like 1
GCL Glutamate-Cysteine Ligase
GCLC Glutamate-Cysteine Ligase Catalytic
GCLM Glutamate-Cysteine Ligase Modulator
GR Glutathione reductase
GRP78 Glucose-Regulated Protein 78
GSCs Glioma Stem Cells
GSH Glutathione
GSK3 Glycogen synthase kinase-3
GSS Glutathione synthetize
GSSG Oxidized glutathione

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GST	Glutathione S-Transferase
HCC	Hepatocellular Carcinoma
HO	Heme Oxygenase
IL	Interleukin
iNOS	Induced Nitric Oxide Synthase
IR	Irradiation
IRE1	Inositol-requiring enzyme1
JNK	Jun NH2-terminal kinase
KEAP1	Kelch-Like-Ech-Associated Protein 1
KIR	Keap1-Interacting Region
LC3B	light chain 3B
MAPK	Mitogen-activated protein kinase
MDR	Multidrug resistance-associated proteins
MMP-9	Metalloproteinase-9
MRP1	Multidrug-resistance-associated protein-1
MSCs	Mesenchymal Stem Cells
mTOR	Mammalian target of rapamycin
mTORC	Mammalian target of rapamycin complex
NADPH	Adenine Dinucleotide Phosphate
Neh	Nrf2-ECH homology
NFE2	Nuclear factor erythroid-derived 2
NF-E2	Nuclear Factor-Erythroid 2
NFE2L2	NFE2 like BZIP Transcription Factor 2
NQO1	Nad(P)H:Quinine Oxidoreductase 1
Nrf2	Nuclear Related Factor 2
OX	Electrophiles
PDI	Protein Disulfide Isomerase
PERK	Protein kinase RNA-like ER kinase
PGD	Phosphogluconate Dehydrogenase
PHGDH	Phosphoglycerate Dehydrogenase
PI3K	Phosphoinositide 3-Kinase
POMP	Proteasome Maturation Protein
PPARγ	Peroxisome Proliferator-Activated Receptor Gamma
PPP	Pentose Phosphate Pathway
PSAT1	Phosphoserine Aminotransferase-1
RAC3	Receptor-Associated Co-Activator 3
Rb	Retinoblastoma
RIDD	Regulated Ire1 Dependent Decay
RNS	Reactive Nitrogen Species
ROS	Reactive Oxygen Species
ROS/RS	Reactive Oxygen and Nitrogen Products

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RXRα	Retinoid X receptor alpha
SERCA	Calcium transport ATPase
SHMT2	Serine Hydroxymethyltransferase-2
shRNAs	Small hairpin RNA
Simva	Simvastatin
Sirt6	Sirtuin 6
SLC7A11	Solute carrier 7A11
sMAF	Small musculoaponeurotic fibrosarcoma
SMRT	Silencing mediator for retinoid and thyroid hormone receptor
SOD	Superoxide Dismutase
SP1	Specificity Protein 1
TFs	Transcription Factors
TGF-β	Transforming growth factor
TKT	Transketolase
TME	Tumor microenvironment
TMZ	Temozolomide
TNBC	Triple-Negative Breast Cancer
TNF-α	Tumor Necrosis Factor
TRAF2	Tumor Necrosis Factor Receptor-Associated Factor-2
TRB3	Tribbles-Related Protein3
Trx	Thioredoxin
TSC2	Tuberous Sclerosis Complex 2
UGT	Udp-Glucuronosyltransferase
ULK	Unc-51-Like Kinase
UPR	Unfolded Protein Response
VEGF	Vascular Endothelial Growth Factor
XBP1	X-Box-Binding Protein-1
β-TrCP	β-transducin repeat-containing E3 ubiquitin protein ligase

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