Nrf2 is a potential therapeutic target in radioresistance in human cancer

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Abstract

Radiation therapy can effectively kill cancer cells through ROS generation. Cancer cells with upregulated antioxidant systems can develop high radioresistance ability, and the transcription factor NF-E2-related factor 2 (Nrf2) is a key regulator of the antioxidant system. Currently, there are numerous data indicating the important role of Nrf2 in cancer radioresistance. In this review, we summarize the aberrant regulation of Nrf2 in radioresistant cells and discuss the effects and underlying mechanism of Nrf2 in promoting radioresistance. These findings suggest that Nrf2 might be a potential therapeutic target in cancer radiation resistance or a promising radioprotector for normal organs during radiation therapy in the future.

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Keywords: Nrf2; Radioresistance; ROS; Antioxidant; Targeted therapy

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1. Introduction

Reactive oxygen species (ROS) are implicated in diverse cellular processes, including metabolism and signaling, and they play important roles in a variety of diseases, including cancer. ROS can be produced by physical or chemical stimuli [1,2]. ROS are toxic at high levels in mammalian cells and cause DNA damage and membrane oxidative damage [3]. Ionizing radiation has been shown to significantly contribute to the generation of ROS in a variety of cells, and it can induce DNA damage and repair, apoptosis, cell cycle control, signal transduction, and oxidative stress responses inside the cell [4,5]. Radiation therapy is now commonly accepted as one of the most effective treatment for a variety of malignant cancers of different origins and stages [6]. Radiation therapy can effectively kill cancer cells through ROS generation. However, some cancer cells with upregulated redox and antioxidant ability can escape from the damaging effects of radiation by scavenging ROS, leading to radioresistance [7,8]. Therefore, it is urgent to solve the radioresistance of these cancer cells to improve the curative effect of cancer therapy. Studies have shown that upregulating antioxidant enzyme expression protects cancer cells from radiation therapy, whereas blocking these defense systems confers increased sensitivity [7,9,10]. The expression of these antioxidant enzymes is mostly regulated by the transcription factor NF-E2-related factor 2 (Nrf2). Nrf2, a member of the cap’n’collar family of basic leucine zipper transcription factors, is an essential activator of the coordinated transcription of genes encoding antioxidant enzymes and phase II detoxifying enzymes through the antioxidant response element (ARE) [11]. In this review, we will focus on the role of Nrf2 in regulating the radioresistance of human cancer and its potential as a target for radiation therapy in cancer.

2. The main mechanism of radioresistance in human cancer

Radiation therapy is one of the most widely accepted and effective cancer treatments, and it induces apoptosis in cancer cells through the induction of direct and indirect DNA damage [12]. Direct DNA damage is caused by ionizing photons and ionizing particles, whereas free radicals derived from ionized water molecules contribute to indirect DNA damage [13,14]. Radiation therapy appears capable of successfully controlling many types of cancer, but its effectiveness is severely compromised by the radioresistance acquired by cancers. Based on a review of existing research, the increased radioresistance of cancer cells is generally determined by numerous factors: quiescence propensity, upregulated cell cycle control genes, enhanced DNA repair ability, dynamic and reciprocal interactions with an abnormal stromal microenvironment, and activation of free radical scavenging [15,16]. ROS mediator-induced damage is one of the primary mechanism of cancer cell death by ionizing radiation. Maintaining low ROS levels in cancer is an important mechanism of radioresistance, which acts through the up-regulation of endogenous antioxidant defense mechanisms or enhanced levels of ROS scavengers [17,18]. A number of studies have found that overexpression of antioxidant enzyme occurs in cancer resistance to radiation therapy, whereas blocking these antioxidant defenses can enhance radiation sensitivity and promote radiation-induced apoptosis [19–22].

Recently, cancer stem cells (CSCs) have been recommended as a vital topic of radiation research in radiation oncology [23–27]. CSCs account for a minor subpopulation of the tumor population, but they play an important role in cancer radioresistance [28]. Recent data suggest that CSCs show increased expression of free radical scavenging or antioxidant defense systems, which contribute to a lower cellular ROS levels [8]. These results also indicate that enhancing the cellular defense system against ROS, such as the Nrf2 antioxidant pathway, is the critical mechanism of CSC radioresistance.

3. The role of Nrf2 in radioresistance

Nrf2 is a key transcriptional regulator of genes encoding numerous cytoprotective enzymes, and it is induced by environmental and endogenously derived oxidative/electrophilic agents [29,30]. Under basal conditions, Nrf2 is sequestered by the repressor Kelch-like ECH-associated protein 1 (Keap1) in the cytoplasm and rapidly degraded in a ubiquitin-proteasome-dependent manner, whereas Nrf2 escapes Keap1-mediated repression under conditions of oxidative stress [31,32]. Nrf2 protects cells/tissues against damage from environmental oxidative stressors and xenobiotics because it regulates the expression of antioxidant and phase II drug-metabolizing enzymes [32–34]. Indeed, many cancers express gain-of-function Nrf2 mutants or loss-of-function Keap1 mutations that result in constitutive Nrf2 activation [30,35,36], which contributes to the resistance against oxidative stress and xenobiotics, such as chemotherapeutic drugs and ionizing radiation, in cancer cells [9,37]. Furthermore, recent studies have revealed that suppression of the Nrf2-mediated antioxidant defense system confers sensitivity to ionizing radiation and chemotherapeutic drugs [9,10,30].

3.1. Aberrant Nrf2 regulation confers radioresistance to cancer

Singh et al. [35] reported an analysis of the genomic sequence of Keap1 in 12 cell lines and 54 non-small-cell lung cancer (NSCLC) samples. The sequence data revealed somatic mutations in Keap1 in a total of 6 cell lines and 10 tumors at a frequency of 50% and 19%, respectively. As expected, Keap1 mutations induced Nrf2 activation, resulting in the enhanced induction of antioxidants, xenobiotic metabolism enzymes, and drug efflux pumps. Then, the
overactivation of Nrf2-mediated defense systems leads to cancer cell protection from their inherently stressed microenvironment and anti-cancer treatments [30]. This finding was also confirmed by other reports which showed that loss-of-function mutations in Keap1 led to increased Nrf2 activity in several cancers, including lung cancer [35,36,38,39], breast cancer [40,41], gall bladder cancer [42], prostate cancer [9], ovarian cancer [43], and colorectal cancer [44]. In addition to Keap1 mutations, gain-of-function mutations of Nrf2 were also observed in many cancer cells lines and cancer tissues, leading to the aberrant activation of Nrf2 by blocking Nrf2–Keap1 binding [30,45,46].

3.2. Relationship between radiosensitivity and Nrf2 target gene expression in cancer

3.2.1. HO-1

Heme oxygenase-1 (HO-1), a member of the family of heat shock proteins (HSP32), is detected in most mammalian tissues at low levels but is up-regulated in response to a variety of stress stimuli, including UV irradiation, nitric oxide and hypoxia [47–51]. HO-1, which is a target gene of Nrf2 [52], is overexpressed in various types of human cancers, including renal cell carcinoma, colorectal cancer, pancreatic cancer, gastric cancer, bladder cancer, and NSCLC [53–59]. The biological roles of HO-1 are believed to provide a growth advantage in cancer cells and contribute to cellular resistance against anticancer treatment through anti-oxidative and anti-apoptotic effects [55,59]. The relationship between responsiveness to radiation therapy and HO-1 expression has been studied in many studies. In the report of Berberat et al., human pancreatic cancer samples showed marked HO-1 expression in cancer cells and cancer-associated immune cells, and HO-1 expression was strongly induced after radiation in pancreatic cancer cell lines [55]. In addition to the growth-promoting functions of HO-1, the authors found that the targeted knockdown of HO-1 expression made cancer cells significantly more sensitive to radiation therapy [55]. Meanwhile, Nrf2 was also found to be up-regulated in pancreatic cancer cell lines and ductal adenocarcinomas, and RNA interference (RNAi) depletion of Nrf2 caused enhanced sensitivity to γ-irradiation [60]. The role of HO-1 in radioresistance was also confirmed in an endothelioma cell line. Ewing et al. [61] showed that the induction of HO-1 conferred radioresistance to cancer cells through inhibiting irradiation-induced apoptosis, whereas this protective effect could be reversed by blockade of HO-1 function with tin protoporphyrin IX (SnPP), which acts as an HO-1 inhibitor. Paradoxically, a study on human esophageal squamous cell carcinomas (ESCCs) suggested that HO-1 expression was associated with a higher sensitivity of esophageal cancer patients to radiation therapy [62]. However, Nrf2 gain-of-function mutations were consistently detected in samples from advanced ESCC patients and ESCC cell lines [45,63], and short hairpin RNA-mediated down-regulation of Nrf2 revealed that the mutant Nrf2 contributed to γ-irradiation resistance in ESCC cells [63]. Therefore, we hypothesize that HO-1 regulation mediated by Nrf2-independent pathways could also be relevant to the inconsistent radiosensitivities in ESCCs, as the Nrf2-independent induction of HO-1 was previously reported in differentiated keratinocytes (KC) [64,65]. Further research is needed to determine the downstream genes of Nrf2 that are associated with the resistance of ESCC patients to radiation therapy and whether the role of HO-1 in radioresistance is cancer type dependent.

3.2.2. NQO1

NAD(P)H dehydrogenase, quinone 1 (NQO1), another Nrf2-regulated gene, is also involved in radioresistance. NQO1 activity is ubiquitously present in all tissue types, and it can be activated by xenobiotics, antioxidants, oxidants, and ionizing radiation [66,67]. The expression of NQO1, as well as Nrf2, was found to be dramatically increased in prostate cancer DU-145 cells, which are resistant to radiation therapy [9]. On the contrary, hematopoietic stem cells (HSCs) with low NQO1 mRNA levels might be rather radioresistant as suggested by the significant correlation between the surviving fraction of HSCs and their intrinsic NQO1 expression after 6 h of X-irradiation [68]. There are two possible explanations for these different results: (1) in the better survived HSCs, more NQO1 was exhausted during the NQO1-mediated protection against ROS after irradiation and (2) it may be dependent on the different characteristics of stem cells and cancer cells.

3.2.3. Prx1

Peroxiredoxins (Prxs) are thiol-specific antioxidant proteins that are classified largely on the basis of having either one (1-Cys) or two (2-Cys) conserved cysteine residues [69]. Prx1, a major member of the 2-Cys subfamily, is also a target gene of Nrf2 [70]. Reports showed that decreasing Prx1 expression through different methods causes an augmentation of radiosensitivity [71]. That is, Prx1 activation can enhance the radioresistance of cancer cells [72,73].

3.2.4. Mdm2

The basal expression of murine double minute (Mdm2) gene, which functions as an inhibitor of p53, can be regulated by Nrf2 through the ARE [74]. The novel evidence showed that the inhibition of Nrf2 could suppress Mdm2 expression, which might result in enhanced p53 signaling [74]. Mdm2 is often overexpressed in human tumors. And re-activation of p53 by Mdm2-inhibition contributes to the radiosensitization of colon cancer cells [75]. Another study also suggested that regulation of Mdm2-expression should be a promising treatment strategy for relative radioresistant prostate cancer [76]. However, it needs to seek direct evidence on whether the Nrf2 takes part in the radioresistance modulation of Mdm2.

3.2.5. Others

Ferritin heavy polypeptide 1 (FTH1), glutamate-cysteine ligase catalytic subunit (GCLC), glutamate-cysteine ligase
modifier subunit (GCLM), glutathione reductase (GSR), and thioredoxin reductase 1 (TXNRD1) are also target genes of Nrf2 [68]. Kato et al. [68] found that the mRNA expression levels of FTH1, GSR and TXNRD1 increased significantly after X-irradiation in CD34+ cells prepared from HSCs, but no significant difference was observed in GCLC and GCLM. Further research confirmed that down-regulating these genes enhanced radiosensitivity. However, the relationship between radioresponse and the expression of these genes requires further research [77].

3.3. Cross-talk between Nrf2 and other genes related to radioresistance

3.3.1. HIF-1

Hypoxia acts as a microenvironmental factor that affects tumor growth and progression by enhancing tumor angiogenesis [78,79] and increases the generation of ROS as a potent Nrf2 inducer [80]. The hypothesis that hypoxic cancer cells were resistant to radiation therapy was proposed by Gray et al. in 1953, which highlighted the importance of the tumor microenvironment in determining clinical outcome [81]. The radioresistance of hypoxic cells has been attributed to the low oxygen concentration in those cells, which should reduce the ROS production by irradiation. On the other hand, the induction of angiogenesis by hypoxia would be another factor explaining the radioresistance of hypoxic cancers by helping cancer growth, although reoxygenation of cancer tissues by angiogenesis could also sensitize the cancer cells by simulating ROS production in cancer cells [82]. Subsequently, hypoxia-inducible factor 1 (HIF-1) was recognized as the major transcriptional regulator of hypoxia-induced angiogenesis through the transactivation of genes encoding multiple angiogenic growth factors [83]. The tumor vasculature represents an important target of radiation therapy through the regulation of endothelial cell apoptosis [84]. HIF-1 is composed of HIF-1α and HIF-1β, and the levels of HIF-1α expression are the primary determinant of HIF-1 DNA binding and transcriptional activity [85]. Oropharyngeal cancer patients with HIF-1α overexpression showed a worse prognosis after radiation therapy [86]. In contrast, HIF-1 knockdown suppressed hypoxia-induced radioresistance while increasing radiosensitivity in glioma xenografts [87]. In a study by Moeller et al., the authors demonstrated that HIF-1 may be a major determinant of cancer radiosensitivity [88]. HIF-1 acts through secreting cytokines, including vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF), capable of inhibiting radiation-induced endothelial cell (EC) apoptosis [88]. A review by Zhou et al. presented the cross-talk between HIF-1α and Nrf2, which is responsible for HIF-1α-mediated angiogenesis in ECs [89]. Moreover, Nrf2 blockade can suppress colon cancer angiogenesis by inhibiting the hypoxia-induced activation of HIF-1α-VEGF signaling [90]. In contrast, Nrf2 may directly affect the biological behavior of intratumoral ECs through pro-angiogenetic effects [89]. Accordingly, it can be assumed that Nrf2 may play a role in radioresistance through regulating HIF-1α-induced angiogenesis signaling or EC survival.

3.3.2. NF-κB

The transcription factor nuclear factor-kappa B (NF-κB) is activated by many different stimuli, binds to specific DNA sequences in target genes, and regulates the transcription of genes involved in immunoregulation, growth regulation, inflammation, carcinogenesis, and apoptosis [91]. Many reports have detected the activation of NF-κB in radioresistant cells [92–96]. Conversely, NF-κB down-regulation by different inhibitors enhances the radiosensitivity of radioresistant cells [97–101]. In addition to hypoxia, chronic inflammation has also emerged as one of the hallmarks of cancer and also plays a pivotal role in modulating cancer radiation responsiveness [102]. NF-κB provides a mechanistic link between inflammation and cancer radioresistance [103]. The interplay between Nrf2 and NF-κB signaling pathways has been studied by Nair et al. Their results reflect the cross-talk between Nrf2 and NF-κB modulated through the MAPK cascade in the inflammation-associated etiopathogenesis of cancer [104]. Further research is needed to explore whether there is an interaction between Nrf2 and NF-κB in the cellular response to radiation therapy and what acts as a bridge between them.

3.3.3. p21Cip1/WAF1

p21Cip1/WAF1 is the first cyclin-dependent kinase (CDK) inhibitor to be identified as a mediator of p53 in DNA damage-induced growth arrest, cell senescence, and direct CDK regulation [105]. The relationship between p21Cip1/WAF1 overexpression and radioresistance suggests that p21Cip1/WAF1 might be a potential suppressor of radiation-induced apoptosis in cancer, including cervical carcinoma [106], glottic cancer [107], and head and neck squamous cell carcinomas (HNSCCs) [108]. In addition to its p53-dependent mechanism, p21Cip1/WAF1 may play a p53-independent role in the radioresistance of human gliomas [109]. p21Cip1/WAF1 may act through other functions, such as the regulation of nuclear import, transcriptional activation, and the regulation of apoptosis [110]. Radiation-induced oxidative stress has been confirmed clinically [111]. In response to oxidative stress, p21Cip1/WAF1 is upregulated to provide cell protection against apoptosis [112,113]. p21Cip1/WAF1-dependent cell survival under oxidative stress is mediated through Nrf2 activation by stabilizing the Nrf2 protein [114]. As described by Chen et al. [114], the 5′4KRR motif in p21Cip1/WAF1 directly interacts with the 29DLG and 79ETGE motifs in Nrf2 and thus competes with Keap1 for Nrf2 binding, compromising the Keap1-dependent ubiquitination of Nrf2. Additionally, p21Cip1/WAF1-induced cell protection against radiation-induced apoptosis may occur through the activation of the Nrf2 antioxidant pathway, and this regulation may be a principal mechanism of p21Cip1/WAF1-mediated radioresistance.
Table 1
Studies on radiation sensitization with Nrf2 down regulation in vitro and in vivo.

<table>
<thead>
<tr>
<th>Cell types</th>
<th>Agent/method</th>
<th>Inhibition mechanism</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate cancer cells (in vitro)</td>
<td>Nrf2-shRNA</td>
<td>Knockdown of Nrf2</td>
<td>[9]</td>
</tr>
<tr>
<td>NSCLC cells (in vitro and/or in vivo)</td>
<td>IM3829</td>
<td>Inhibition of Nrf2-binding activity and HO-1, NQO1 expression</td>
<td>[10]</td>
</tr>
<tr>
<td>Pancreatic cancer cells (in vitro)</td>
<td>Nrf2-siRNA</td>
<td>Knockdown of Nrf2</td>
<td>[60]</td>
</tr>
<tr>
<td>Esophageal squamous cancer (ESC) (in vitro)</td>
<td>Nrf2-shRNA</td>
<td>Knockdown of Nrf2</td>
<td>[63]</td>
</tr>
<tr>
<td>Mouse lymphocytes (in vitro)</td>
<td>Nrf2-shRNA</td>
<td>Knockdown of Nrf2</td>
<td>[128]</td>
</tr>
<tr>
<td>Immortalized mouse embryonic fibroblast cells (MEF) (in vitro and/or in vivo)</td>
<td>Nrf2-deficient cells</td>
<td>Loss of Nrf2 function</td>
<td>[129]</td>
</tr>
<tr>
<td>NSCLC cells (in vitro)</td>
<td>Nrf2-shRNA</td>
<td>Knockdown of Nrf2</td>
<td>[130]</td>
</tr>
<tr>
<td>Head and neck squamous carcinoma and cerebral glioma</td>
<td>6-Aminonicotinamide (6-AN) and 2-deoxy-d-glucose (2-DG)</td>
<td>Deregulation of Nrf2–Keap1 signaling</td>
<td>[131]</td>
</tr>
</tbody>
</table>

3.3.4. ATM

Ataxia-telangiectasia (A-T) is an autosomal recessive disease characterized by early normal brain development followed by progressive neurodegeneration. The gene that is mutated in A-T (ATM) is a serine protein kinase that functions as a critical regulator of the cellular DNA damage response [115]. Many studies have demonstrated the connection between ATM protein expression and radioresistance [116–118]. The ATM gene, a sensor of DNA damage and oxidative stress, activates a wide variety of effectors involved in multiple signaling pathways, such as cell cycle checkpoints, DNA repair and apoptosis [118]. Moreover, recent advances from several studies have also underscored the cross-talk between Nrf2 and ATM during oxidative stress. For example, Li et al. [119] suggested that ATM regulates Nrf2 via protein kinase C delta (PKCδ) in oxidative stress response. Thus, we propose that the ATM interaction with Nrf2 may contribute to radioresistance via promoting antioxidant protection against radiation-induced oxidant damage.

3.4. The role of Nrf2 in cancer stem cells radioresistance

Cancer stem cells (CSCs), which are characterized by stem cell properties and exist in most cancers, have been an important area of radiation research for over half a century [28,120–122]. CSCs are responsible for cancer radioresistance, and one important mechanism is their enhanced ability to scavenge ROS and free radicals, leading to the escape of cell death due to radiation therapy [8,15,16,123]. The redox balance contributes to the maintenance of stem cell self-renewal and differentiation [8,124,125]. Similar to normal stem cells, CSCs also contain lower ROS levels than corresponding non-tumorigenic cells [8,126], which seems to be associated with the elevated expression of antioxidant systems. Glutathione (GSH) is an intracellular reducing molecule with antioxidant activity, and the level of GSH is significantly related to CSC radioresistance [8]. Moreover, the glutamate-cysteine ligase catalytic subunit (GCLC), which was found to catalyze GSH synthesis, is also a target gene of Nrf2 [127]. Therefore, Nrf2 represents a redox-sensitive transcription factor implicated in CSC radioresistance.

4. Targeting Nrf2 to overcome radioresistance

The gain of Nrf2 function by a dysfunctional Keap1–Nrf2 interaction or other inducers has been implicated in the

Table 2
Nrf2 inhibitors.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Mechanism and target</th>
<th>Effect</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luteolin</td>
<td>Reduction of Nrf2 levels at both the mRNA and the protein</td>
<td>Chemotherapy Sensitizer in A549 cells</td>
<td>[132]</td>
</tr>
<tr>
<td>Wogonin</td>
<td>Downregulation of the Nrf2-dependent response</td>
<td>Chemotherapy Sensitizer in MCF-7/DOX cells</td>
<td>[133]</td>
</tr>
<tr>
<td>Brusatol</td>
<td>Inhibition of the Nrf2-mediated defense mechanism</td>
<td>Chemotherapy Sensitizer in A549 xenografts</td>
<td>[134]</td>
</tr>
<tr>
<td>Glycogen synthase kinase-3β (GSK-3β)</td>
<td>Phosphorylation and nuclear elimination of Nrf2</td>
<td>Induction of sensitization to external insults such as oxidant injury</td>
<td>[135]</td>
</tr>
<tr>
<td>E-cadherin</td>
<td>Inhibition of nuclear accumulation of Nrf2 by β-catenin-binding domain</td>
<td>Chemotherapy Sensitizer in HepG2 cells</td>
<td>[136]</td>
</tr>
<tr>
<td>Keap1 complementation</td>
<td>Increases of Nrf2 degradation</td>
<td>Chemotherapy Sensitizer in Biliary tract cancer (BTC) cells</td>
<td>[44]</td>
</tr>
<tr>
<td>Caveolin-1 (Cav-1)</td>
<td>Inhibition of expression of antioxidant enzymes through direct interaction with Nrf2</td>
<td>Induction of sensitization to oxidant injury</td>
<td>[137]</td>
</tr>
<tr>
<td>The Cullin 3 ubiquitin E3 ligase (Cul3)</td>
<td>Negative regulation of Nrf2</td>
<td>Induction of Mcf-7 cells sensitization to chemotherapy or oxidative stress</td>
<td>[138]</td>
</tr>
</tbody>
</table>
resistance of cancer cells to radiation therapy. Thus far, strategies to inhibit the levels and/or activity of Nrf2 have been developed and used in studies on Nrf2 to improve the efficiency of radiation therapy. As shown in Table 1, increasing evidence demonstrates that Nrf2 down-regulation facilitates the re-sensitization of cells to ionizing radiation. The currently available Nrf2 inhibitors, including some proteins and drugs, are summarized in Table 2. These inhibitors may be further studied as sensitizers for the radioresistance of cancer cells. On the other hand, some studies have explored the possibilities that Nrf2 activation before exposure can be applied as a radioprotector in normal tissue. For example, 1,4-naphthoquinone (NQ) exhibited complete protection against radiation-induced cell death in lymphocytes postirradiation by activating Nrf2-mediated cell cytoprotection [128]. However, in MEF cells, Nrf2 activation by sulforaphane, 2′-tert-butylhydroquinone (tBHQ) and phenyl isocyanate (PEITC) before irradiation was not radioprotective in vitro or vivo [129]. These conflicting results require more studies to explore whether Nrf2-inducing agents or prooxidants can be utilized as a radioprotector for normal organs, such as the spleen and liver.

5. Conclusions and perspectives

In conclusion, Nrf2 is believed to play an important role in cancer radioresistance, and the possible mechanisms of Nrf2 in radioresistance are shown in Fig. 1. Aberrantly increased Nrf2 activity or expression occurs in cancer cells, conferring radioresistance. The up-regulation of Nrf2 target genes, such as HO-1, NQO1 and Prx1, has also been confirmed in relation to cancer radioresistance. The mechanisms of Nrf2 in radioresistance include not only Nrf2 target gene activation but also cross-talk between Nrf2 and other radioresistance-related genes, including HIF-1, NF-kB, p21Cip1/WAF1 and ATM. In addition, Nrf2 provides a large contribution to the radioresistance of CSCs, which are a cornerstone of the
cancer radioresistance mechanism. Interestingly, Nrf2 activation confers cancer radioresistance, but this may turn into radioprotection in normal cells, leading to decreased radiation injury.

Considering the importance of Nrf2 in radiation therapy, novel therapeutic approaches targeting the Nrf2 activity of cancer cells, especially in cancers with Nrf2 over-expression, deserve further investigation. Inhibition of the Nrf2-mediated antioxidant pathway, especially by Nrf2 activity inhibition, may be a feasible strategy to improve the radiation response of radioresistant cancer. The inhibition of Nrf2 expression by Nrf2 knockdown or compounds has shown promising results in vivo and in vitro. Other compounds with chemotherapy-sensitizing activity, which act by inhibiting Nrf2 activity, should be studied as radiosensitizers. It is our expectation that Nrf2-targeted drugs will be applied in the clinic to improve the outcome of radiation therapy, and Nrf2 inducers can be used for protecting normal organs against radiation injury.

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