Molecular pathways associated with oxidative stress and their potential applications in radiotherapy (Review)

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Abstract. Radiotherapy is an essential and effective treatment modality for cancer. Excessive levels of reactive oxygen species (ROS) induced by ionizing radiation disrupt the redox homeostasis and lead to oxidative stress that may result in cell death. However, the tumor cell microenvironment is dynamic and responds to radiotherapy by activating numerous cellular signaling pathways. By scavenging excess ROS, the activity levels of the endogenous antioxidant enzymes result in radioresistance and worsen the clinical outcomes. To assess the full potential of radiotherapy, it is essential to explore the underlying mechanisms of oxidative stress in radiotherapy for potential target identification. The present review article summarized recent data demonstrating nuclear factor-erythroid factor 2-related factor 2 (Nrf2) as a powerful transcription factor and one of the major cellular defense mechanisms that protect against oxidative stress in response to radiotherapy; the glutathione (GSH) and thioredoxin (Trx) systems complement each other and are effective antioxidant mechanisms associated with the protection of cancer cells from radiation damage. In addition, it is suggested that dual targeting to inhibit GSH and Trx enzymes may be a potential strategy for the development of radiosensitive and radioprotective drugs.

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1. Introduction

Oxidative stress generally originates from toxic by-products resulting from the imbalance between radicals and antioxidants, which primarily arises from the accumulation of reactive oxygen species (ROS) (1,2). The redox balance is maintained by complex cellular biochemical and genetic mechanisms. Redox imbalance may have profound effects on physiological and pathophysiological mechanisms (3,4). ROS disrupt cellular processes by non-specific modifications on critical amino acid residues in proteins (resulting in protein oxidation), fatty acids in lipids (to cause lipid peroxidation) and nucleic acids (inducing DNA damage and strand breaks) (5-8). ROS mainly includes the superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), hydroxyl radical (·OH) and singlet oxygen ($^1O_2$) (9). Among these, ·OH is the most reactive ROS and is able to react with almost any tissue directly, thereby causing more effective cellular damage than any other ROS (10). Under pathological conditions, tumor cells produce elevated levels of ROS compared with those of normal cells (11-13). Tumor cells always adjust their metabolism to increase intracellular ROS levels and maintain their survival and proliferation during tumorigenesis (14,15). However, ROS have a dual role in cancer development. ROS may lead to epigenetic alterations that promote the acceleration of tumor progression. By contrast, higher levels of ROS promote genome instability, inducing activation of cancer cell death or inhibiting resistance to anticancer treatment (16-19).

Theoretically, radiotherapy is able to more precisely target the tumor. The relative toxicity caused by radiation to the

surrounding normal tissues is limited (20). However, several antioxidant transcription factors may be activated in response to radiotherapy, resulting in the inhibition of ROS-dependent damaging effects induced by radiation and in the reduced effectiveness of the treatment (21). In addition, the source of ROS is considered to be a double-edged sword, which has a key initiator role in ionizing radiation (IR)-associated normal tissue injury (22). The radioresistance and tumor recurrence following radiotherapy are significant problems to overcome, which may contribute to treatment failure and tumor relapse. Specific modifications in the production of ROS and the concentrations of antioxidants have pivotal roles in cancer radiotherapy (12,23,24). Current research demonstrates that targeting oxidative stress may benefit patients with radiation resistance during radiotherapy (25). Therefore, the identification of the mechanisms of oxidative stress has been the focus of various studies. In the present review article, the mechanisms underlying the regulation of oxidative stress induced by radiotherapy were summarized and the benefits of using radio-protectors or radio-sensitizers were discussed.

2. Molecular mechanisms and pathways of oxidative stress

The current literature was reviewed and oxidative stress-related genes were extracted from pertinent papers (Table SI). Finally, 198 gene symbols were confirmed with the HUGO Gene Nomenclature Committee Multi-symbol checker tool (https://www.genenames.org/tools/multi-symbol-checker). Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis by R software was used to identify the signaling pathways that were mainly enriched by oxidative stress-related genes. Fig. 1 indicates the significant pathways identified (rich factor >0.1), which were sub-grouped by the KEGG main class. The top significant pathways with roles in cellular processes were as follows: Ferroptosis, apoptosis, p53 signaling pathway, mitophagy, cellular senescence pathway and autophagy. In addition, the forkhead box protein O (FoxO), Erb-b receptor tyrosine kinase (ErbB), vascular endothelial growth factor receptor (VEGF), hypoxia inducible factor-1 (HIF-1), TNF, mTOR, NF-κB, MAPK, 5'AMP-activated protein kinase, Janus kinase/signal transducer and activator of transcription, Ras and PI3K/AKT signaling pathways were the most represented pathways according to environmental information processing. Glutathione (GSH) metabolism was dominant in the metabolism category.

As protectors of cancer cells from the effects of ROS, the superoxide dismutase (SOD), GSH reductase (GPX), thioredoxin (Trx) reductase (TrxR) and catalase (CAT) antioxidant enzymes were investigated, which have a major role in ROS scavenging (26-28). Fig. 2 indicates the response of the antioxidant system to radiotherapy. SODs may function in different cellular compartments to rapidly catalyze O_2^- into H_2O_2 and O_2. The other antioxidant enzymes, including CAT, GPX and TrxR, convert H_2O_2 into water (29). In mammalian cells, the following three types of SOD exist: A copper and zinc SOD termed CuZn-SOD or SOD1, which is mainly found in the cytosol, a manganese SOD, termed Mn-SOD or SOD2, which is found in the mitochondrial matrix, and an extracellular SOD termed EC-SOD or SOD3 (30). CAT is located primarily in the peroxisomes and is a widespread and highly efficient antioxidant enzyme present in almost all living organisms, which uses either iron or manganese as a cofactor (31). The GSH system, which is composed of glutathione reductase (GR), GSH and NADPH, is the most abundant cellular thiol antioxidant system and is regulated by its biosynthesis, redox state and cellular export (32). Its redox cycle is regulated by GPX and GR (33). At least eight isoforms of GPX enzymes (GPX1-GPX8) have been found in mammals, of which GPX4 is the only one that is able to reduce phospholipid hydroperoxides (34,35). The solute carrier family 7 member 11 (SLC7A11) has a pivotal role in intracellular cysteine balance and GSH biosynthesis (36). Similar to the GSH system, Trx is another powerful cellular disulfide reductase involved in the control of cellular redox homeostasis, which comprises TrxR, Trx and NADPH (37). The mammalian Trx consists of the following three isoforms: Trx1 in the cytosol, Trx2 in the mitochondria and a testis-specific Trx. The following three types of TrxRs have been characterized: Cytosolic TrxR1, mitochondrial TrxR2 and testis-specific TrxR3 (38). Trx donates electrons to peroxyredoxin (Prx) to remove H_2O_2. Typically, the Trx and GSH systems are functioning in parallel, and several types of reciprocal crosstalk have been identified between these two systems, indicating that the components of one system may be a backup to those of the other (38).

3. Functional characterization of oxidative stress in radiotherapy

Radiotherapy has been recognized as one of the mainstay regimens for various types of cancer treatment (39,40). The changes in the biological effectiveness of the targeted tissues caused by IR are related to the energy deposits observed in the encountered molecules of specific cell signaling pathways (41,42). Oxidative stress has a powerful function in cancer progression and in the response to radiotherapy. IR-induced cell damage may originate from direct or indirect actions. Direct damage to the cell mainly relies on the radiation that affects the DNA molecules and results in the formation of either single- or double-strand breaks (43). By contrast, water radiolysis rapidly produces ROS; the elevated intracellular levels of ROS cause oxidative stress, which results in indirect damage. Approximately 80% of the cellular content is composed of water, which has a leading role in IR-induced biological effects (42,44).

The radiolysis of water leads to the formation of free radicals, such as hydrated electrons (e^-_{aq}), ·OH, and H·, and certain molecular products (H_2, H_2O_2) (45,46). e^-_{aq} are able to indirectly form O_2^- with molecular oxygen (47). In addition, H_2O_2 and O_2^- may be transformed into the highly reactive ·OH via the Fenton or the Haber-Weiss reactions in the presence of transition redox metals, such as iron or copper (48). IR generates ROS that readily interact with cellular membrane lipids, proteins and nucleic acids, resulting in the alteration of membrane permeability, proteolytic degradation, DNA damage and genomic instability. This eventually induces radiation damage and tumor cell death (49). Consequently, radiotherapy may efficiently induce massive cell death by increasing intracellular ROS levels. Furthermore, the radiation damage also affects adjacent normal cells via the bystander effect (50-52). Radiotherapy used in cancer treatment may

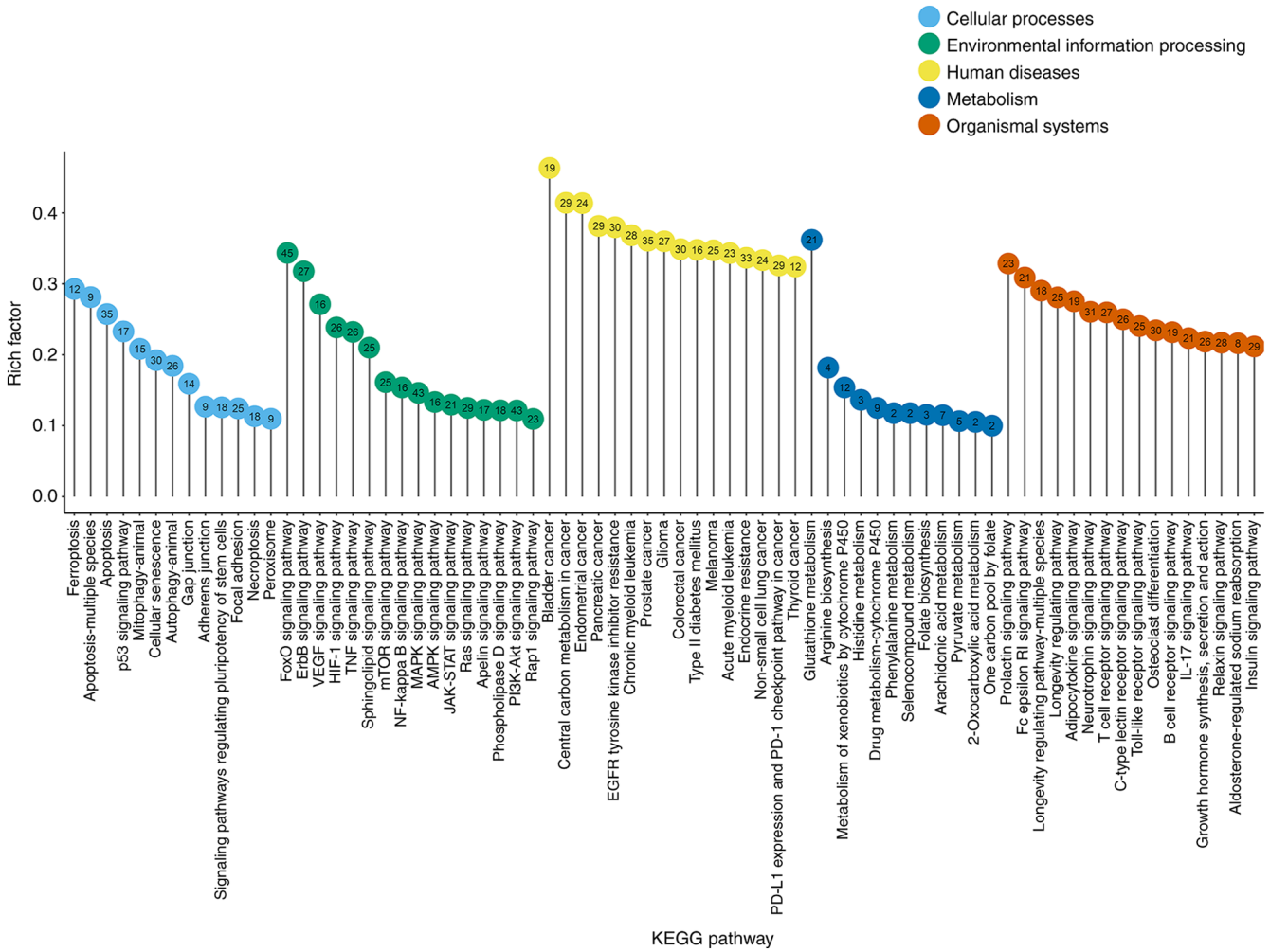

Figure 1. KEGG pathway enrichment analysis of oxidative stress-related genes. The rich factor resembles the ratio of the number of target genes annotated in this pathway. KEGG, Kyoto Encyclopedia of Genes and Genomes.

cause problems in the heart, as well as in the hematopoietic, intestinal and nervous systems (53,54).

4. Activation of oxidative stress pathways by radiotherapy

The results of the KEGG pathway analysis revealed that the dominant pathways that regulate oxidative stress were the ferroptotic (Fig. S1), apoptotic (Fig. S2), FoxO (Fig. S3) and ErbB (Fig. S4) signaling pathways. All of these pathways may be activated by radiotherapy (55-58). To respond to IR-induced oxidative stress and the change in redox environmental conditions, multiple signal transduction pathways crosstalk with each other (Fig. 3). Depending on the IR dose, the dose rate, the quality and the time period of treatment, these mechanisms may affect the antioxidant or pro-oxidant effects in a different manner. To clarify the crosstalk between oxidative stress and the intracellular IR response, the corresponding molecular mechanisms were investigated. These molecular events were involved in the relationship between the major pathways linked to oxidative stress and the response of the antioxidant defense pathways to radiotherapy.

Ferroptotic pathway. Ferroptosis is a recently described form of regulated cell death, which differs from apoptosis and necrosis and is characterized by the accumulation of iron-dependent lipid peroxidation (59,60). The critical role of ferroptosis in radiotherapy has been established in recent studies (55). The cell membrane is the major target of IR-induced ROS, since membrane lipids are easily peroxidized, resulting in structural and functional damage (61). Glutathione metabolism is one of the main mechanisms governing ferroptosis. GPX4 and SLC7A11 are key regulators of glutathione metabolism, which have a crucial role in limiting lipid peroxidation (62).

Radiotherapy results in downregulation of SLC7A11 expression and induces lipid oxidative damage to promote tumor-associated ferroptosis (63). IR may also cause significant downregulation in the expression levels of GPX4 (64). However, in certain cases, IR may induce SLC7A11 or GPX4 expression as an adaptive response to protect cells from ferroptosis (65). In addition, p53 and nuclear factor-erythroid factor 2-related factor 2 (Nrf2) may be rapidly activated by IR, which has an important role in the regulation of ferroptosis. p53 is able to inhibit the cellular uptake of cystine by transcriptionally restricting SLC7A11 expression to reduce antioxidant capacity, resulting in ferroptosis (66,67). The transcription factor Nrf2 is considered to have a central role in the upregulation of the expression levels of specific anti-ferroptotic defense biomarkers. Nrf2 promotes cell survival in irradiated

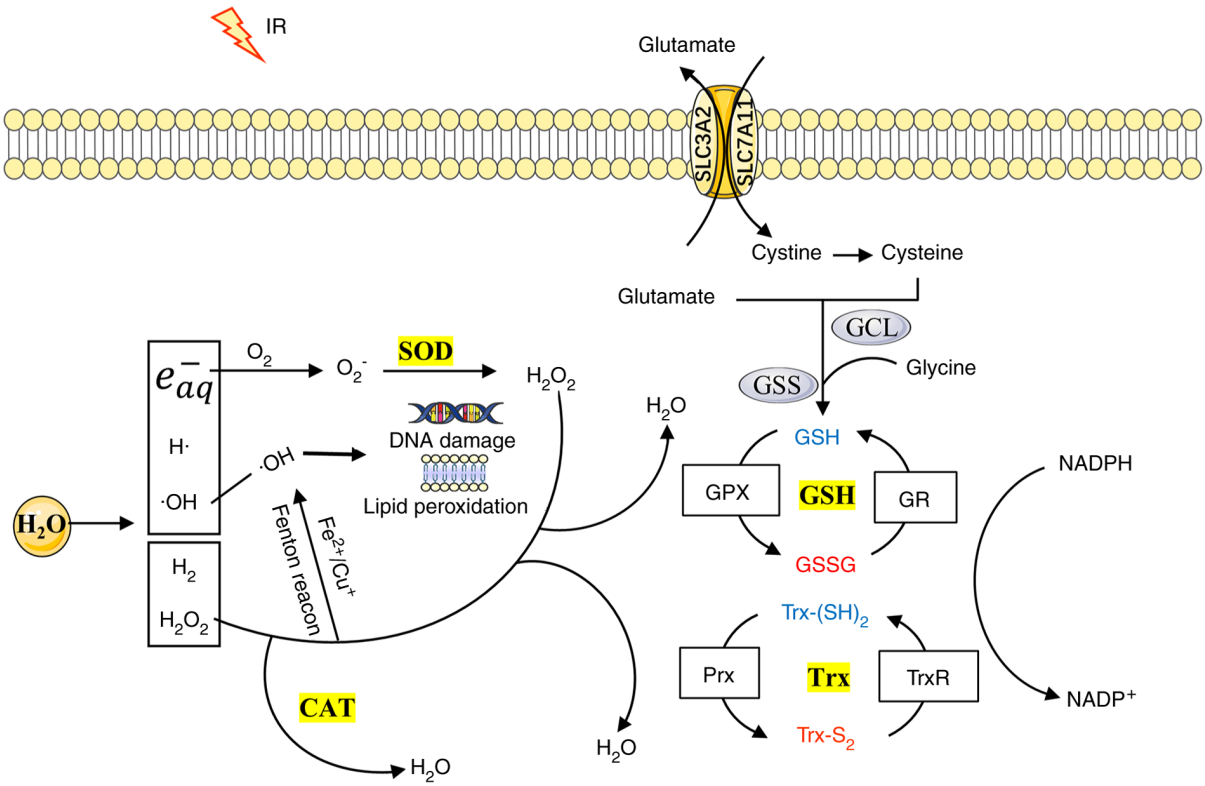

Figure 2. Antioxidant system response to radiotherapy. H_2O_2 is generated through water radiolysis, which may be transformed into the highly reactive OH through the Fenton reaction. SOD is an important metalloenzyme that catalyzes O_2^- to molecular oxygen O_2 and H_2O_2. H_2O_2 may be transformed to H_2O by the enzymes CAT, GPX or TrxR. CAT is a common antioxidant enzyme from the family of oxyreductases. GSH and Trx are two thiol-dependent redox systems acting in concert, which have been identified as powerful antioxidant mechanisms. These enzymes may effectively scavenge H_2O_2. The yellow color corresponds to the four main antioxidant enzyme systems. Oxidized and reduced states are indicated by red or blue color, respectively. H_2O_2, hydrogen peroxide; ·OH, hydroxyl radical; SOD, superoxide dismutase; CAT, catalase; GPX, glutathione peroxidase; Trx, thioredoxin; TrxR, Trx reductase; GSH, glutathione; O_2, molecular oxygen; O_2^-, superoxide anion; GCL, glutamate-cysteine ligase; GSS, GSH synthetase; GR, GSH reductase; Prx, peroxiredoxin; IR, ionizing radiation; SLC3A2, solute carrier family 3 member 2; e^-_{aq}, hydrated electrons.

cells via activation of specific downstream regulator target genes, including SLC7A11. These genes aim to prevent oxidative damage (68-71). In addition, the Trx system may also protect cells from lipid peroxidation (72). Nrf2 is able to bind to the TrxR1 and Trx1 promoter antioxidant responsive element (ARE) and improve its activity (73). In addition, it has been indicated that Nrf2 is able to bind to the ARE sequence of various other antioxidant proteins, namely GPX2, Prx1, Prx6 and glutamate-cysteine ligase catalytic subunit (74-77).

Apoptotic pathway. Apoptosis is a form of regulated cell death. Oxidative stress is considered to be a strong inducer of apoptosis (78). Apoptosis is triggered by the following two major signaling pathways: The extrinsic and the intrinsic pathway. These pathways are independent but interact with each other (79). It is suggested that both the intrinsic pathway (activated by mitochondrial outer membrane permeabilization) and the extrinsic pathway (initiated by plasma membrane receptors) may be activated following IR treatment (80).

However, studies have demonstrated that radiotherapy primarily acts through the intrinsic pathway (80-82). The signatures of several intrinsic pathway proteins are associated with radiosensitivity, such as p53, Bcl-2 and Bax (83,84). In response to IR-induced oxidative stress, p53 has an essential role in the regulation of the redox state (85,86). The activation of p53 is largely dependent on the ATM kinase that phosphorylates p53 shortly after IR (87). A previous research study suggested that p53 regulated radiotherapy efficacy by targeting Bcl-2 proteins to release Bax, which in turn promoted apoptosis or inactivated invasiveness (88). In addition, p53 was also able to activate the expression levels of SOD2 and GPX1 by binding to their promoters, which stimulates an antioxidant response (89). It is known that TNFα is a potent pro-apoptotic molecule, which promotes the expression of several inflammatory factors. However, TNFα also has a role in cell survival mechanisms (90-92). TNFα is able to increase the transcription of GPX4 (93). Activation of the transcription factor NF-κB has a central role in regulating apoptosis (94). In addition to its apoptotic activity, NF-κB induces the expression of specific genes, which may attenuate ROS production and promote survival (95). For instance, the NF-κB pathway may lead to SOD2 gene activation (96,97). Experimental evidence also suggests that GPX4 is transcriptionally regulated by NF-κB (93).

FoxO signaling pathway. The FoxO family includes several pivotal transcription factors activated in response to oxidative stress, such as FoxO1, FoxO3a, FoxO4 and FoxO6. The majority of previously published studies have focused on the first three members (98,99). The interaction of FoxO and p53 proteins may coordinate tumor suppression via the regulation of various common target genes, such as p21, growth arrest

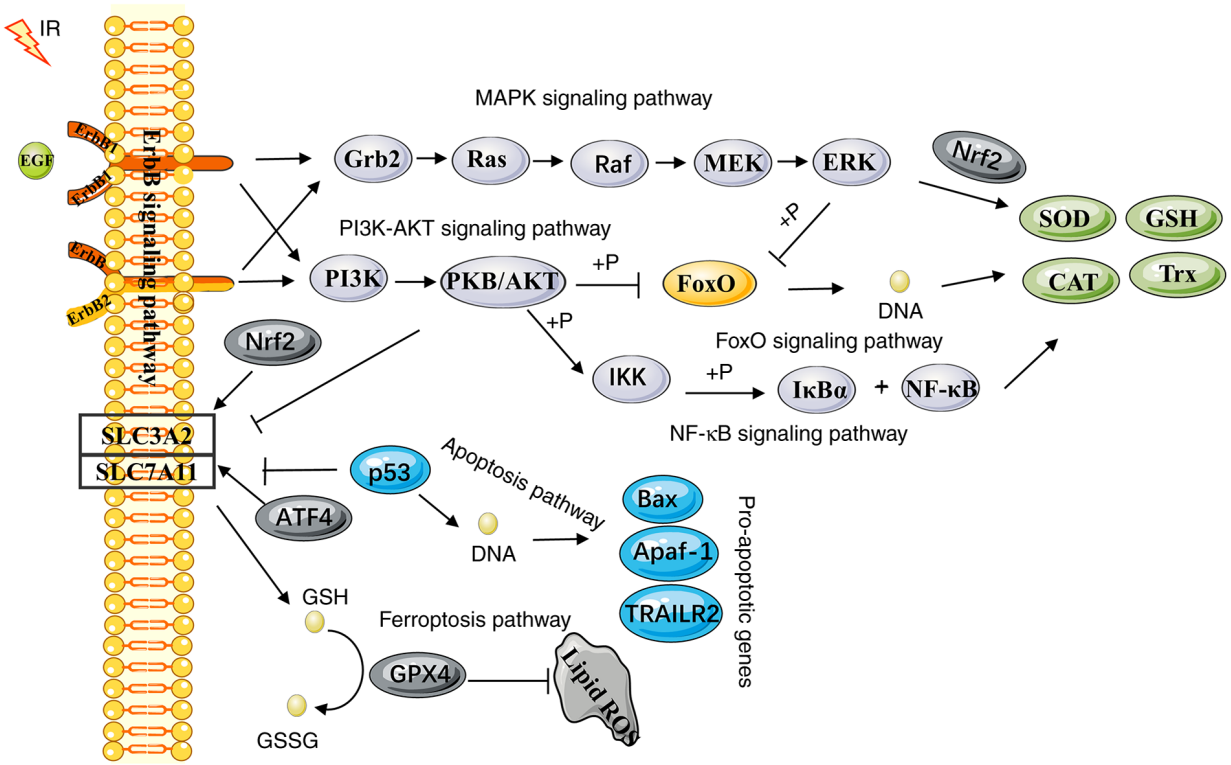

Figure 3. Activation of oxidative stress-related pathways by radiotherapy. In response to IR, activated ErbB1 and ErbB2 (via interaction with one of the ligand-bound partners) induce the subsequent activation of downstream signaling pathways that include MAPK, PI3K/AKT and FoxO. The activation of the MAPK and PI3K/AKT signaling pathways increases the expression levels of Nrf2, thereby activating several antioxidant systems in response to oxidative stress. The FoxO-target genes include various genes encoding antioxidant proteins, which have a complex role in the induction of oxidative stress. It may not only activate the antioxidant system to promote tumor cell survival, but also promote apoptosis. NF-κB is another key pathway regulating the fine balance of the cellular redox status. The binding of the NF-κB proteins to DNA regulates the transcription of various potential antioxidant targets. In addition, IR activates the SLC7A11/GPX4 axis, which is considered to be one of the most important means of regulating oxidative stress via the ferroptotic pathway. IR, ionizing radiation; ErbB, Erb-b receptor tyrosine kinase; FoxO, forkhead box protein O; SLC7A11, solute carrier family 7 member 11; GPX4, glutathione reductase 4; SOD, superoxide dismutase; CAT, catalase; Trx, thioredoxin; Nrf2, nuclear factor-erythroid factor 2-related factor 2.

and DNA damage, protein phosphatase 1D and sestrin 1 (57). A previous study revealed that JNK is able to phosphorylate FoxO1, FoxO3a, and FoxO4 to facilitate nuclear entry of FoxO, leading to the upregulation of the expression levels of antioxidant genes (98).

FoxO3a is a crucial effector of IR-induced apoptosis in response to genotoxic stress (100). FOXO3a promotes the cell survival pathway by directly binding to the SOD2 promoter, causing increased expression of SOD2. The activation of the latter protects the cells from oxidative stress-mediated injury (101). By contrast, FoxO3a may effectively increase cellular antioxidant capacity by enhancing the levels of CAT and Prx3 to protect against oxidative stress (102,103). However, the regulation of oxidative stress by FoxO3a is complex. A previous study indicated that depletion of FoxO3a expression profoundly reduced kelch-like ECH associated protein 1 protein levels, thereby activating Nrf2 signaling (104). It was also indicated that FoxO4 was able to bind to the SOD2 promoter to upregulate SOD2 expression (105). FoxO1 was able to promote activating transcription factor 4 expression, which acts as an important transcription factor for SLC7A11, leading to GSH synthesis (106,107).

ErbB signaling pathway. The ErbB family of proteins is also termed the epithelial growth factor receptor (EGFR) family and consists of the four following members: EGFR (ErbB1 or Her1), ErbB2 or Her2, ErbB3 or Her3, and ErbB4 or Her4 (108). In response to IR, the ErbB receptor tyrosine kinase family is rapidly activated, leading to subsequent activation of multiple downstream pathways (58,109). The activated downstream pathways mainly include PI3K/AKT, MAPK/ERK1/2, Ras and the mTOR signaling pathways, leading to alteration in cell proliferation, apoptosis, autophagy, migration and invasion (110-112). The EGFR transactivation caused by ROS results in the protection of the cells against oxidative stress with extensive crosstalk occurring among these pathways (113).

ErbB receptors, notably EGFR and ErbB2, are closely associated with the induction of oxidative stress (114). EGFR may stimulate HIF signaling activity to improve cellular survival (115). A previous research study has identified a functional transcription start site for GPX3, which is used for binding with HIF-1 (116). Several mechanisms have also been reported to explain the increase in Nrf2 transcription by the PI3K/AKT and Kras signaling pathways (117). The study also indicated that ErbB2 activated Nrf2 transcriptional activity through direct protein-protein interactions, which caused the induction of the expression of antioxidant and detoxification proteins (118). Moreover, Sakurai *et al* also reported that overexpression of Nrf2 augmented the TrxR1 promoter

Table I. Regulation of radiotherapy by targeting antioxidant enzyme systems.

Gene name	Targeting antioxidant system	Mechanism of effect	(Refs.)
SLC7A11	GSH system	Contributes to GSH synthesis	(65)
GPX4	GSH system	Converts GSH into oxidized glutathione	(65)
Nrf2	Trx system	Targets Trxr1 activity	(73,119)
Nrf2	Trx system	Targets Trx1 activity	(73)
Nrf2	Trx system	Targets Prx1 activity	(75)
Nrf2	GSH system	Targets Prx6 activity	(76)
Nrf2	GSH system	Targets GPX2 activity	(74)
Nrf2	GSH system	Targets GCLC activity	(77)
Nrf2	GSH system	Targets SLC7A11 activity	(71)
HIF-1	GSH system	Targets GPX3 activity	(116)
NF-κB	GSH system	Targets GPX4 activity	(93)
NF-κB	SOD system	Targets SOD2 activity	(96,97)
TNFα	GSH system	Targets GPX4 activity	(93)
p53	GSH system	Targets GPX1 activity	(89)
p53	SOD system	Targets SOD2 activity	(89)
FoxO3a	SOD system	Targets SOD2 activity	(101,103)
FoxO4	SOD system	Targets SOD2 activity	(105)
FoxO3a	Trx system	Targets Prx3 activity	(102,103)
FoxO3a	CAT system	Targets CAT activity	(102,103)

GSH, glutathione; HIF, hypoxia-inducible factor; ErbB, Erb-b receptor tyrosine kinase; FoxO, forkhead box protein O; SLC7A11, solute carrier family 7 member 11; GPX4, glutathione reductase 4; SOD, superoxide dismutase; CAT, catalase; Trx, thioredoxin; Trxr, Trx reductase; Nrf2, nuclear factor-erythroid factor 2-related factor 2; Prx, peroxiredoxin.

activity (119). In addition, it has been demonstrated that the restriction of ErbB2 receptor contributes to cell death through the production of ROS (120).

It is important to note that IR-induced ROS leads to cellular oxidizing stress that has an important role in radiotherapy. Several proteins are related to the regulation of the antioxidant systems. These proteins control the expression of various antioxidant genes and may defend against the induction of oxidative stress by IR (Table I). Consequently, the effects of various types of anticancer treatment may be diminished.

5. Oxidative stress acts as a mediator of radiosensitivity

IR-induced oxidative stress is not only involved in cancer cell death but also in the activation of the damage-repair and survival signaling to relieve the induction of oxidative damage. These activations are responsible for radioresistance in cancer (85). The inhibition of oxidative stress appears to be the main mechanism, established by the intracellular antioxidant system, responsible for tumor radioresistance (121). As presented in Table II, increasing evidence has demonstrated that antioxidant system inhibitors promote radiation sensitization.

Previous studies have suggested that Nrf2 is a key transcription factor that regulates the expression of various antioxidant proteins (122,123). Nrf2 inhibitors may be an effective approach against radioresistance. ML385 is a specific Nrf2 inhibitor that binds this transcription factor and blocks the downstream target gene expression, leading to the sensitization of breast cancer stem cells to IR (124). Brusatol selectively reduces the protein levels of Nrf2 by enhancing ubiquitination and degradation of Nrf2 and enhances the radiosensitivity of tumors (125). In addition, IM3829 markedly enhances the radiosensitivity of human lung cancer cells by inhibiting the mRNA and protein expression levels of Nrf2 (126). Halofuginone, a less-toxic febrifugine derivative, is considered to be particularly promising for cancer treatment. This compound rapidly suppresses the accumulation of the Nrf2 protein in therapy-resistant cancer cells (127). Although FoxO3a may be activated by IR, leading to an increase in the expression levels of antioxidant markers, FoxO3a-induced apoptosis has received increasing attention in response to radiation. Butyrate (128) and resveratrol (129) have demonstrated the potential to overcome the radioresistance effect by enhancing the activation of FoxO3a transcription. During radioresistance, ferroptosis inducers also have a key role. A previous study revealed that sulfasalazine (inhibitor of SLC7A11) and RSL3 (inhibitor of GPX4) exert significant radiosensitizing effects *in vitro* (65). TrxR inhibitors enhance radiosensitivity by triggering excessive oxidative stress. Specific examples of these compounds include auranofin (72,130), platinum complexes (20) and selenadiazole (131,132). Since Trx and GSH perform crosstalk with each other, their dual inhibition has synergetic antitumor effects in cancer therapy by inducing ROS production (133). EGFR or ErbB2 inhibitors (e.g. lapatinib) led to increased radiosensitivity in wild-type K-ras pancreatic cancer (134). The EGFR inhibitor icotinib has been indicated to increase radiosensitivity by enhancing apoptosis

Table II. Summary of targeting antioxidant system agents as radiosensitizers.

Name	Mechanism of effect	Types of cancer	Stages of development	(Refs.)
Sulfasalazine	Inhibits SLC7A11	Lung cancer	*In vivo* (A549, patient-derived xenograft)	(65)
RSL3	Inhibits GPX4	Lung cancer	*In vitro* (A549)	(65)
Auranofin	Inhibits Trxr	Liver cancer, breast cancer	*In vitro* (Huh7, HepG2), *In vivo* (4T1, EMT6)	(72,130)
Platinum complexes	Inhibits Trxr	Melanoma	*In vitro* (A375)	(20)
Selenadiazole	Inhibits Trxr	Melanoma, cervical cancer	*In vitro* (A375, HeLa)	(131,132)
ML385	Inhibits Nrf2	Breast cancer	*In vitro* (SUM149, SUM159)	(124)
IM3829	Inhibits Nrf2	Lung cancer	*In vitro* (H1299, A549)	(126)
Brusatol	Inhibits Nrf2	Lung cancer	*In vitro* (A549)	(125)
Halofuginone	Inhibits Nrf2	Lung cancer	*In vitro* (A549), *In vivo* (A549)	(127)
Butyrate	Activates FoxO3a	Colorectal cancer	*In vitro* (primary cancer)	(128)
Resveratrol	Activates FoxO3a	Cervical cancer	*In vitro* (HeLa)	(129)
Lapatinib	Inhibits EGFR or ErbB2	Pancreas adenocarcinoma	*In vivo* (Capan-2)	(134)
Icotinib	Inhibits EGFR	Lung cancer	*In vivo* (H1650)	(135)
APG-115	Inhibits MDM2-p53	Gastric cancer	*In vivo* (MKN45)	(136)

SLC7A11, solute carrier family 7 member 11; ErbB, Erb-b receptor tyrosine kinase; FoxO, forkhead box protein O; GPX4, glutathione reductase 4; Trxr, thioredoxin reductase; Nrf2, nuclear factor-erythroid factor 2-related factor 2; EGFR, epithelial growth factor receptor.

and downregulating the MAPK-AKT and ERK signaling pathways (135). In addition, combination treatment with radiotherapy and an MDM2-p53 inhibitor (APG-115) made tumors overcome radioresistance and enhance the antitumor effects (136).

6. Antioxidants act as radioprotective agents

Typically, IR causes the accumulation of endogenous ROS in irradiated cells, as a consequence of the activation of intracellular signaling pathways (137-139). These effects result in an ongoing inflammatory cascade, which may contribute to continuous damage that surpasses the initial insult and responses noted in non-irradiated cells, which are neighboring to irradiated cells (IR-induced bystander effects) (140). The side effects of IR mostly result from the increased oxidative stress and inflammation generated during radiotherapy (141). Therefore, it is of particular importance that the induction of tumor cell death during radiotherapy occurs without producing extensive damage to surrounding healthy tissues (142).

To reduce these adverse effects, radioprotectors are employed to protect against IR damage to healthy tissues. These compounds act by different mechanisms, which are mainly associated with the modulation of the antioxidant defense (49). p53 inhibition may reduce damage to normal tissues and this strategy has been experimentally tested in mice by using a small-molecule inhibitor of p53 (pifithrin-α) (143). Isofraxidin may have a radioprotective effect in human leukemia cells through decreasing ROS levels in a p53-independent manner (144). Resveratrol has been indicated to attenuate IR enteritis by inhibiting oxidative stress and apoptosis through the activation of the Sirtuin 1/FoxO3a and PI3K/AKT signaling pathways (145). In addition, the endogenous compounds melatonin and vitamin D are considered to be potent radioprotectors for the protection against oxidative damage caused by IR (146). Melatonin has been reported to possess significant potency in inhibiting the induction of oxidative stress via regulation of the expression levels of certain antioxidant genes (including Nrf2) and the activities of ROS/nitric oxide-producing enzymes (147). In addition, this hormone may directly scavenge free radicals to alleviate oxidative injury induced by IR in different cells or organs (147). In previous studies, plant and plant-derived products, such as herbal medicine, have been extensively examined for their effectiveness and compatibility in conferring radioprotection (49). Mn porphyrins are powerful SOD mimics, which have been indicated to possess radioprotective effects in different cells, animal models and tissues, including the lung, the prostate and the brain (148,149). The lead Mn porphyrins, such as MnTE-2-PyP^{5+} (BMX-010, AEOL10113), MnTnBuOE-2-PyP^{5+} (BMX-001) and MnTnHex-2-PyP^{5+} have entered clinical trials for the assessment of their efficacy in the radioprotection of normal tissues during cancer radiotherapy (149).

7. Conclusions

Accumulating evidence suggests that a rational combination of antioxidants or oxidants with IR is an attractive approach to improve the tumor treatment response. In the present review article, the molecular pathways and potential candidate targets that control the induction of oxidative stress in radiosensitivity and radioprotection were discussed. Nrf2 was identified as a key transcriptional target involved in the resistance of cancer

cells to radiotherapy. In addition, Trx and GSH complement each other. They are parts of powerful antioxidant mechanisms connected with the protection of cancer cells from radiation resistance. However, due to the limitations of the present study, further experiments should be performed to completely uncover the roles of these antioxidant enzyme systems in radiotherapy. A deeper understanding of the mechanisms underlying oxidative stress in cancer radiotherapy may reveal novel therapeutic opportunities.

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Availability of data and materials

All data generated or analysed during this study are included in this published article.

Authors' contributions

RL and YB contributed to the preparation, bioinformatics analyses and drafting of the manuscript. RL, YB, LL and LCL performed the relevant literature search, assisted in obtaining data and revised the manuscript. XDL and SMM supervised the preparation of the manuscript and critically reviewed the manuscript. All authors have read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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