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REVIEW

Radiation-activated prosurvival signaling pathways in cancer cells

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Abstract

Radiation therapy is a standard treatment for local disease control of solid tumors. Although radiation therapy has significantly improved the overall survival and quality of life of cancer patients, its efficacy has been limited by the development of radiation resistance and the presence of residual disease after therapy, leading to cancer recurrence. Radiation induces cytotoxicity in cancer cells, mainly by causing DNA damage. However, concurrently radiation can also activate multiple protective signaling pathways, such as ataxia telangiectasia mutated/ataxia telangiectasia mutated and Rad3-related protein, phosphoinositide-3-kinase/protein kinase B, extracellular signal-regulated kinase, and nuclear factor-κB, which promote cell cycle checkpoint activation, leading to cell cycle arrest/DNA repair and inhibition of apoptosis. Conjointly, these signaling pathways protect cancer cells by reducing the magnitude of radiation-induced cytotoxicity and promoting radioresistance of cancer cells. Thus, targeting these prosurvival pathways could have great potential for sensitizing cancer cells to radiation therapy. In the present review, we summarize the current literature on the radiation-activated prosurvival signaling pathways that promote radioresistance.

KEYWORDS

apoptosis, cell cycle checkpoint, DNA repair, radiation therapy, signaling pathways

1 | INTRODUCTION

Radiation therapy (RT) is a staple approach for local disease control in cancer treatment. When combined with chemotherapy, named chemoradiation, RT provides additional benefits, such as better disease control and significantly improved cancer patient survival.[1–3] However, radioresistance and the presence of residual disease after RT remain major problems that impede the effectiveness of RT.[4–7] Currently, no clinical approach is available for either predicting the benefit of radiation therapy for individual cancer patients or for radiosensitization of cancer cells. Thus, a clear understanding of the molecular mechanisms that promote cancer cell survival in response to RT could lead to identifying therapeutic targets for developing rational pharmacological strategies to improve the efficacy of RT.

Ionizing radiation (IR) activates numerous cellular responses, including apoptosis, autophagy, cellular senescence, cell cycle arrest, and DNA repair (Figure 1).[8] Among the radiation-induced prosurvival signaling pathways, some are involved in the induction of cell cycle arrest and promoting DNA repair, whereas others are engaged in the inhibition of apoptosis induction.[9,10] These pathways act synergistically to protect cancer cells from radiation-induced cytotoxicity, thereby promoting the development of radioresistance. This review summarizes the signaling pathways that positively regulate cancer cell survival in response to IR.

2 | RADIATION ACTIVATES CELL CYCLE CHECKPOINT SIGNALING THAT PROMOTES CELL CYCLE ARREST AND DNA REPAIR

2.1 | Cell cycle response signaling pathways

The cytotoxicity caused by IR is mainly the result of DNA damage. Radiation induces several forms of DNA damage, which include

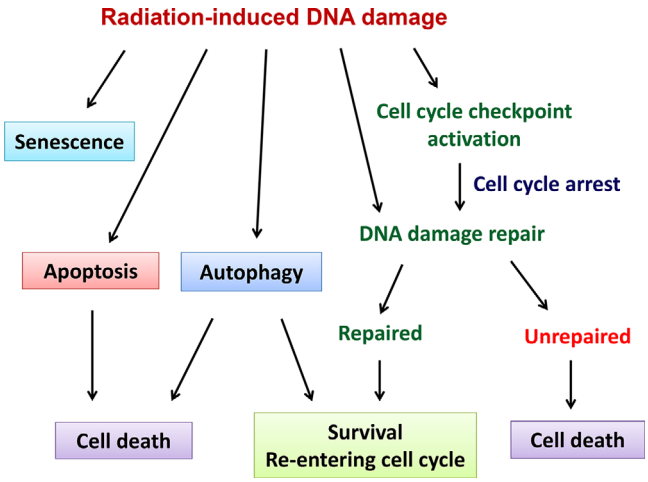

FIGURE 1 Cellular response to ionizing radiation. In response to ionization radiation, the cancer cell will undergo DNA damage in the form of single-strand breaks and double-strand breaks. DNA damage sensed by cells results in various cellular responses: senescence, apoptosis, autophagy, cell cycle arrest, and DNA damage repair. Signaling pathways activated by ionizing radiation that promote cell cycle arrest, DNA repair, and inhibition of apoptosis protect cancer cells from radiation-induced cytotoxicity, leading to radiation resistance

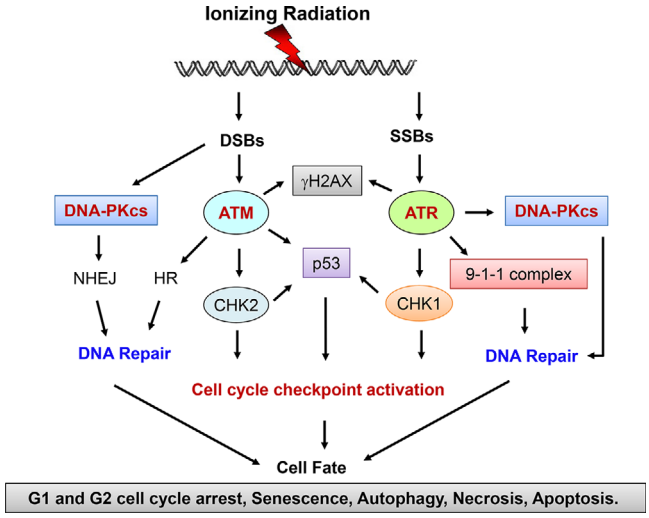

FIGURE 2 Core factors in DNA damage response and DNA repair networks. Ionizing radiation causes DNA damage that activates ataxia telangiectasia mutated (ATM)/ataxia telangiectasia mutated and Rad3-related (ATR)/DNA-PK (red bold), which transmit signals to downstream targets that regulate DNA repair by non-homologous end-joining repair (NHEJ) and homologous recombination (HR), and activate checkpoint response pathways that arrest the cell cycle or trigger apoptotic pathways, all of which regulating cell fate. DSBs, double-strand breaks; SSBs, single-strand breaks

single-stranded DNA breaks (SSBs), DNA double-strand breaks (DSBs), sugar and base modifications, and DNA-protein crosslinks.[11,12] Among those, DSBs are the most deadly form of DNA damage, as unrepaired DSBs can lead to the lethality of cells.[13–15]

In response to DNA damage, cell cycle checkpoints become activated to block cell cycle progression to allow time for cells to repair the damage.[16] Depending on the phase of the cell cycle at which the damage is sensed, the cells can be blocked at the G1/S border, intra-S, or G2/M border of the cell cycle.[16] If the damage is irreversible or the cell cycle checkpoint is dysfunctional, apoptosis might be triggered to eliminate the injured cells.[16] Thus, properly functioning cell cycle checkpoints promote cell survival by counteracting the cytotoxicity of DNA damage.

Ataxia telangiectasia mutated (ATM)- and ataxia telangiectasia mutated and Rad3-related (ATR)-mediated signaling pathways play essential roles in the radiation-induced cell cycle checkpoint responses (Figure 2).[16,17] In response to IR-induced DNA damage, ATM and ATR kinases are rapidly activated, which, in turn, activate their respective downstream targets, including DNA-PKcs, p53, and Chk1/Chk2 kinases.[16,17] Activation of Chk1 and Chk2 results in phosphorylation of Cdc25, leading to its subcellular sequestration, degradation, and/or inhibition of Cdc25 that normally activates Cdc2/cyclin B at the G2/M boundary.[18] Both Chk1 and Chk2 can also activate p53 after radiation.[16,17,19] Activation of p53 by ATM, ATR, Chk1, and Chk2 kinases leads to the induction of p21 protein, which can directly inhibit the activities of the Cdk4/cyclin D, Cdk6/cyclin D, and Cdc2/cyclin A/B complexes.[16,17]

The G1/S transition is controlled by the activity of Cdk4/6 kinases coupled with cyclin D, the activities of which are predominantly regulated by the p53/p21 pathway.[20] The G2/M border is tightly controlled by the Cdc2/cyclin B complex, whose activity is required for the G2/M transition of the cell cycle.[21] The G1 checkpoint is defective in most cancer cells, commonly due to mutations/alterations of key regulators of the G1 checkpoint (p53, cyclin D, etc.),[20] whereas activation of the G2 checkpoint is rarely impaired in cancer cells, as this checkpoint operates primarily through a p53-independent mechanism.[22] In fact, in cancer cells lacking a functional G1 checkpoint, abrogation of the G2 checkpoint often radiosensitizes the cells.[23]

Previous studies identify Cdc2-Y15 residue as an essential site involved in G2 checkpoint activation in response to IR.[24] Cdc2-Y15 is located in the adenosine triphosphate-binding domain of the Cdc2 kinase, and Cdc2-Y15 phosphorylation results in the inhibition of Cdc2, whose activity is required for the G2/M transition of the cell cycle. Cdc2-Y15 is phosphorylated by the Wee1 and Myt1 kinases, and dephosphorylated by the Cdc25 dual-specificity phosphatases.[25–27] Cdc2-Y15 phosphorylation is induced in response to IR exposure, and maintained during IR-induced G2/M arrest.[24,28,29]

In summary, radiation-induced cell cycle checkpoint response signaling pathways promote cell cycle arrest, leading to DNA repair, which, in turn, contributes passively to cell survival in response to radiation.

2.2 | DNA repair pathways

The DNA damage caused by IR activates several phosphoinositide-3 kinase-related kinases, including ATM, ATR, and DNA-PK, which transduces and amplifies the DNA damage signal, thereby triggering the

assembly of DNA repair apparatuses at the damaged sites and initiating DNA repair (Figure 2).[10] DSBs are repaired by one of two competing mechanisms: non-homologous end-joining repair (NHEJ) and homologous recombination (HR), with both mechanisms regulated by phosphoinositide-3 kinase-related kinases.[10] Without sequence homology required, NHEJ rejoins the free ends in a process that commonly produces errors at the point of junction.[30] Each of the two ends is recognized by the Ku70/Ku80 heterodimer, which then recruits DNA-PKcs.[30] Once formed, these complexes bring the ends together for further processing and ligation by DNA ligase IV.[30] In contrast to NHEJ, HR repairs DSBs accurately and with very high fidelity.[30] Although NHEJ functions through the cell cycle, HR mainly operates during the S and G2 phases and repairs DSBs by taking advantage of sequence information present in the intact sister chromatid.[30] Radiation also produces SSBs, mainly through base oxidation by reactive oxygen/nitrogen species (ROS/RNS).[13] The repair of this type of damage uses base excision repair, which removes the damaged base using DNA glycosylase and AP endonuclease, and then fills up the nick through the actions of DNA polymerases and DNA ligase.[31] Subsequently, successful repair of DNA damage promotes cell survival in response to IR, whereas a failure to repair the damaged DNA enhances the cytotoxicity of IR, leading to cell death.

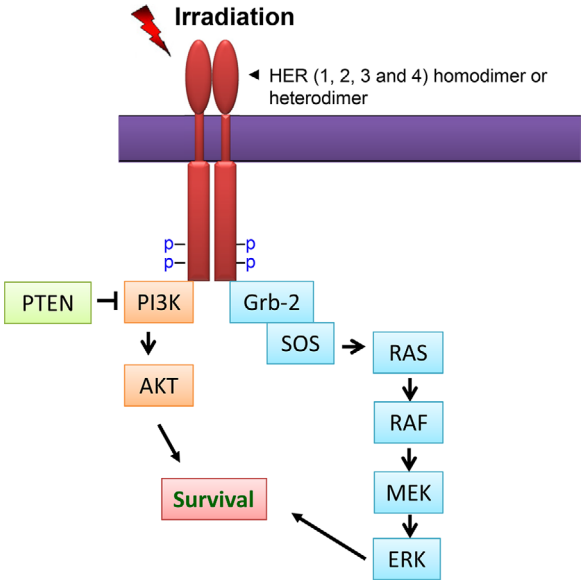

FIGURE 3 Radiation induces activation of HER receptors, which, in turn, lead to the activation of phosphoinositide-3-kinase/protein kinase B (PI3K/AKT) and RAS/RAF/MEK/extracellular signal-regulated kinase (ERK) signaling pathways that promote cell survival

3 | RADIATION–ACTIVATED PROSURVIVAL SIGNALING PATHWAYS

3.1 | Human epidermal growth factor receptor tyrosine kinase-mediated signaling pathways

The human epidermal growth factor receptor (HER) family of receptor tyrosine kinases (RTKs) consists of HER1, HER2, HER3, and HER4, which localize to the cell membrane.[32] HER RTKs share a similar protein structure that contains an extracellular region (ligand binding and dimerization domains), a transmembrane region, and an intracellular region (protein tyrosine kinase domain and phosphorylation regulatory tail).[33] Among HER receptors, HER2 has no known ligand and HER3 possesses very low kinase activity.[33] Binding of ligands to the ligand-binding domain of HER1, HER3, and HER4 results in homo- or heterodimerization of the receptors, followed by transphosphorylation of several tyrosines in the c-terminal regulatory tail of the receptors.[33] The phosphorylated tyrosines form docking sites for downstream adaptors and signal transducers, thereby activating downstream signaling pathways including phosphoinositide-3-kinase (PI3K)/AKT, Rat Sarcoma Virus (RAS)/Rapidly Accelerated Fibrosarcoma (RAF)/Mitogen-activated protein kinase kinase (MEK)/extracellular signal-regulated kinase (ERK), phospholipase C-γ/protein kinase C and Janus kinase (JAK)/Signal Transducer and Activator of Transcription (STAT) pathways.[34,35] Among those pathways, PI3K/AKT and RAS/RAF/MEK/ERK cascades have been shown to promote cell survival in response to radiation (Figure 3).[36]

An increase in epidermal growth factor receptor (EGFR)/HER1 phosphorylation, indicative of HER activation in response to IR exposure, has been reported previously.[37–39] Our most recent work in human breast cancer cells showed that IR results in an increase in phosphorylation of not only HER1, but also HER2, HER3, and HER4.[40] Although the mechanisms responsible for this phosphorylation of HER receptors has not yet been determined, previous studies have shown that receptor protein tyrosine phosphatases, which suppress HER RTK phosphorylation, can be effectively inhibited by ROS/RNS through oxidation stress.[41] Previous studies have also shown that radiation induces ROS/RNS production through a mitochondria-dependent mechanism.[42] Thus, the ROS/RNS production in response to radiation could lead to the inhibition of protein tyrosine phosphatases, which, in turn, results in the activation of HER RTKs. Future studies will be required to examine the possibility of HER receptor activation by radiation.

Inhibition of HER RTKs has been shown to increase the radiosensitivity of cancer cells. Inhibition of HER RTKs by HER pan-inhibitor CI-1033 enhances the radiosensitivity of human colon carcinoma cells both *in vitro* and *in vivo*,[43] whereas EGFR/HER1 inhibition by gefitinib and HER2 inhibition by Herceptin, respectively, radiosensitize EGFR amplified glioma cells and breast cancer cells.[44,45] Generally, the prosurvival function of HER receptors involves at least two possible mechanisms: (i) activation of AKT and ERK1/2 signaling that protects cells by inhibition of apoptosis induction; and (ii) regulation of the cell cycle checkpoint response to promote DNA repair.[36] Our study showed that HER2 activation after radiation is necessary for the induction of the G2/M DNA-damage checkpoint response.[40] In addition, HER1 has been reported to promote the activation of DNA-dependent protein kinase (DNA-PK), which plays a critical role in the NHEJ-mediated repair of DSBs.[46,47]

3.2 | Ras-related C3 botulinum toxin substrate 1 GTPase-promoted prosurvival signaling pathways in response to IR

Ras-related C3 botulinum toxin substrate 1 (Rac1), a member of the Rho family of GTPases, plays important roles in cell migration and survival.[48] Rac1 exists in either an active GTP-bound state or inactive GDP-bound state.[49] Rac1 is activated by its guanine nucleotide exchange factors, which accelerate GDP to GTP exchange and are inhibited by GTPase-activating proteins, which stimulate GTP hydrolysis.[49] In its active state, Rac1 interacts with downstream effectors to activate numerous signaling pathways.[50,51] Rac1 has been reported to activate ERK1/2 signaling through the PAK1/2 kinases, which phosphorylate Raf1 and MEK1 to facilitate the formation of a Raf/MEK/ERK complex.[52–54] Rac1 also interacts with PI3K to activate PI3K/AKT signaling,[55,56] and plays an essential role in AKT activation after UV or sphingosine-1-phosphate treatment.[57,58] Both AKT and ERK1/2 signaling pathways have been shown to promote survival after IR.[36,59–64] In addition, Rac1 is required for IR-induced ROS production and ATM activation,[36,65,66] which activate the nuclear factor-κB (NF-κB) signaling pathway.[67]

We have reported a novel Rac1 function in the regulation of the IR response of breast and pancreatic cancer cells.[65,66,68] Our results showed that Rac1 is rapidly activated by IR in breast cancer cells and is required for the activation of ATM/ATR-mediated cell cycle checkpoint response and inhibition of apoptosis induction after IR. Similarly, other studies reported that Rac1 deficiency diminishes DNA damage checkpoint response, DNA repair, and survival in response to IR and UV exposure.[69] Furthermore, our studies showed that Rac1 signaling is required for the survival of breast cancer cells following hyperfractionated radiation, a clinical protocol for radiation therapy, suggesting a clinical potential of targeting Rac1 for radiosensitization of breast cancer cells.

3.3 | Radiation-activated ERK1/2 pathway

Several signaling pathways have been reported to activate ERK1/2 signaling in response to radiation. As shown by the present authors and others, the rapid activation of HER family receptors after IR contributes to the activation of ERK1/2 signaling in breast and lung cancer cells (Figure 3).[38,70] Furthermore, this role of HER receptors involves the Ras GTPase that generally becomes activated upon HER receptor activation (mainly HER1 and HER2), whereby ectopic expression of Ras-N17 dominant-negative mutant abolishes the radiation-induced ERK1/2 activation.[71,72] Through recruitment of Grb-2 to the activated HER receptors, Grb-2 becomes activated and forms a complex with SOS protein, which triggers the activation of Ras/Raf/MEK/ERK signaling (Figure 3).[71,72] Furthermore, the activated Ras can induce HER1 ligand production, which, through an autocrine feedback loop, further activates HER1 and subsequent Ras/Raf/MEK/ERK signaling.[73,74] Another mechanism implicated in radiation-induced ERK1/2 activation involves the BRCA1 tumor suppressor. Studies from our laboratory show that the knockdown of BRCA1 expression by shRNA markedly diminishes the activation of ERK1/2 signaling in breast cancer cells after radiation.[75] Conversely, inhibition of ERK1/2 signaling using pharmacological inhibitors or siRNA results in the destabilization of BRCA1 protein in irradiated breast cancer cells.[75] These results suggest a positive feedback loop between ERK1/2 signaling and BRCA1 protein stability in response to IR. Finally, the DNA-damage sensor, ATM, has also been implicated in radiation-activated ERK1/2, since ATM inhibition can partially block radiation-induced ERK1/2 activation.[76] Conversely, inhibition of ERK1/2 signaling can also attenuate radiation-induced ATM phosphorylation, as well as the recruitment of ATM to DNA damage foci, which is another positive feedback loop in the radiation response, this time involving ATM and ERK1/2.[76]

ERK1/2 signaling activation in response to radiation has been shown to play an important role in promoting cell survival in response to radiation.[59–61] After radiation, ERK1/2 is activated through dual tyrosine and threonine phosphorylation by MEK1/2, and the activation, in turn, leads to the phosphorylation/activation of >160 substrates.[77] Some of these substrates are transcription factors that regulate the expression of genes encoding for anti-apoptotic proteins.[77,78] The best characterized anti-apoptotic transcription factors induced by ERK1/2 signaling are the cyclic adenosine monophosphate-responsive element-binding protein and CAAT/enhancer-binding protein-β. In response to radiation, ERK1/2 phosphorylates/activates $p90^{rsk}$ kinase, which in turn activates cyclic adenosine monophosphate-responsive element-binding protein and CAAT/enhancer-binding protein-β, thereby inducing the expression of a number of anti-apoptotic proteins, including Bcl-xL, Mcl-1, and c-FLIPs.[79–81] In addition, ERK1/2 can directly phosphorylate and inhibit a number of pro-apoptotic proteins, including Bad, Bim, and caspase 9.[82–85] Thus, by increasing the expression/activity of anti-apoptotic proteins and inhibiting the activity of pro-apoptotic proteins, the net effect of the radiation-activated ERK1/2 signaling is the inhibition of apoptosis in the irradiated cells.

Studies from our group and others have shown that ERK1/2 signaling activation after radiation is essential for induction of the G2/M DNA damage checkpoint response, which involves its role in the activation of ATR and BRCA1, which are key regulators of the G2/M checkpoint.[59,61,75,86,87] Radiation-induced ERK1/2 signaling has also been associated with the transcriptional upregulation of genes involved in DNA repairs, such as *ERCC1*, *XRCC1*, and *XPC*.[88,89] Furthermore, ERK1/2 signaling has been shown to activate DNA-PK, which plays a critical role in NHEJ-mediated DSB repair, and PARP-1, which recognizes SSBs on damaged DNA.[89–92] In addition, ERK1/2 signaling functions as a positive regulator of ATM-dependent HR DSB repair.[76] Thus, by promoting G2/M cell cycle checkpoint activation and increasing DNA repair, ERK1/2 signaling positively regulates cancer cell survival after radiation. Consistent with these observations, an increasing number of studies have shown that constitutive activation of Ras results in an increase in radioresistance of cancer cells, whereas inhibition of MEK or ERK leads to the radiosensitization of cancer cells.[59,65,86,87]

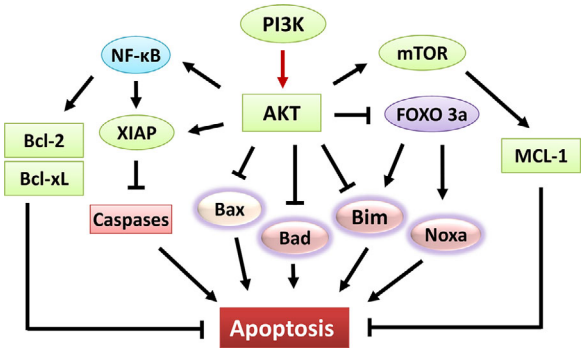

FIGURE 4 Phosphoinositide-3-kinase/protein kinase B (PI3K/AKT)-mediated signaling promotes cell survival. (i) Activation of PI3K by radiation leads to the phosphorylation/activation of AKT; (ii) AKT phosphorylates and inhibits pro-apoptotic proteins Bad, Bax, Bim, and Noxa; (iii) AKT activates prosurvival transcription factor, nuclear factor-κB (NF-κB), resulting in the upregulation of prosurvival genes *BCL-2* and *BCL-XL*; (iv) AKT phosphorylates prosurvival protein, X-linked inhibitor of apoptosis protein (XIAP), which binds and inhibits caspase 3/7/9 that are required for apoptosis induction; (v) AKT phosphorylates/activates mammalian target of rapamycin (mTOR) kinase that phosphorylates and activates anti-apoptotic protein Mcl-1; and (vi) phosphorylation of FOXO3a by AKT results in inhibition and nuclei exclusion of FOXO3a, which upregulates the gene expression of pro-apoptotic proteins, Bim and Noxa

3.4 | PI3K/AKT signaling pathway

The AKT signaling pathway plays a vital role in cell survival. Aberrant activation of this signaling cascade has been detected in various types of malignancies and is associated with tumorigenesis.[93] AKT functions as a prosurvival factor by inhibiting apoptotic signal cascades and activating prosurvival signaling pathways (Figure 4). Upon activation, AKT phosphorylates and inhibits a number of pro-apoptotic members of the Bcl-2 family, including Bad, Bax, and Bim.[94–96] Furthermore, through direct inhibition and exclusion of pro-apoptotic transcription factor Forkhead box O3, AKT also suppresses the transcriptional expressions of the pro-apoptotic factors Bim and Noxa.[97–100]

AKT also positively regulates anti-apoptotic pathways (Figure 4). AKT activates NF-κB transcription factor, which promotes the transcription of a wide range of anti-apoptotic genes, especially *Bd-2* and *Bd-XL*.[101] Furthermore, AKT phosphorylates/activates the prosurvival protein X-linked inhibitor of apoptosis protein, thereby resulting in an increase of binding of X-linked inhibitor of apoptosis protein to caspases 3, 7, and 9, and subsequent inhibition of these caspases, the activities of which are essential for apoptosis induction.[102] Another key prosurvival pathway targeted by AKT is the mammalian target of rapamycin (mTOR) signaling pathway. AKT phosphorylates and activates mTOR kinase, leading to the phosphorylation/activation of the Mcl-1 anti-apoptotic protein.[103,104] Furthermore, AKT negatively regulates hypoxia-induced apoptosis. Radiation therapy often induces hypoxia in tissues that can lead to apoptosis induction in the injured tissue and this hypoxia-induced apoptosis requires glycogen synthase kinase to activate the mitochondria-dependent death-signaling pathway.[105–107] However, AKT activation after radiation can inhibit glycogen synthase kinase activity through phosphorylation, resulting in the activation of glycogen synthesis and glucose transport that suppress apoptosis induction.[108] Finally, AKT is directly involved in the activation of the catalytic subunit of DNA-PK after radiation, thereby promoting NHEJ-mediated DSB repair that increases cell survival.[109] These outcomes establish the role of AKT-mediated signaling pathways in prosurvival response of cancer cells to radiation.

Activation of the PI3K/AKT signaling pathway in response to IR has been commonly observed.[36] A likely mechanism for this activation involves HER RTKs. Upon activation of HER RTKs by radiation, the phosphorylated tyrosines in the carboxyl-terminal regulatory tail of HER3 can form six docking sites for recruitment of the p85 adaptor subunit of PI3K (phosphatidylinositol-3-kinase; Figure 3).[110] Subsequently, the p110 catalytic subunit of PI3K phosphorylates phosphatidylinositol-4,5-biphosphate to generate phosphatidylinositol (3,4,5)-triphosphate, which then leads to the membrane recruitment and activation of proteins that contain a phospholipid-binding (PH) domain, such as phosphoinositide-dependent kinase 1.[111] The activated phosphoinositide-dependent kinase 1 phosphorylates AKT-Thr308, resulting in to the initial AKT activation.[111] The full-activation of AKT requires further phosphorylation of AKT-Ser473 residue by phosphoinositide-dependent kinase 2.[111] Furthermore, mutant K-Ras also positively contributes to the activation of PI3K-AKT signaling in response to radiation through activation of autocrine production of EGFR ligands.[112,113]

The prosurvival function of PI3K/AKT signaling is anticipated to promote the radioresistance of cancer cells. Indeed, cumulative studies showed that the inhibition of PI3K/AKT signaling by either pharmacological inhibitors or genetic approaches results in an enhancement of radiosensitivity of cancer cells both *in vitro* and *in vivo*.[62–64] Furthermore, the increase of radiosensitivity by PI3K/AKT inhibition involves both the diminution of DNA repair and enhancement of apoptosis induction.[62,63,114–116] In contrast, in some cell models, inhibition of PI3K/AKT shows little effect on radiosensitivity, suggesting that PI3K/AKT-independent regulation of radiosensitivity is a probably cell-type dependent phenomena.[20,59,117–119]

3.5 | NF-κB-mediated prosurvival pathways

The NF-κB signaling pathway plays an important role in cell proliferation and survival in response to inflammatory stimuli, including IR, and has been associated with radioresistance (Figure 5).[120,121] At the inactive state, NF-κB is sequestered in the cytoplasm by the inhibitory κB protein (IκB).[121] Upon stimulation by inducers including IR and chemotherapeutics, IκB becomes phosphorylated by IκK kinases and subjected to proteasomal degradation by βTrCP.[121] This releases the sequestered NF-κB, which then translocates into the nucleus to induce targeted gene expressions that promote proliferation and survival.[121] Additionally, IR-induced ATM and ROS can further enhance the activation of the NF-κB pathway.[122] The best validated NF-κB gene targets include Bcl-2, Bcl-xL, and Mcl-1, which are key members of the anti-apoptotic Bcl-2 family. Furthermore, IR activates NF-κB to express cell

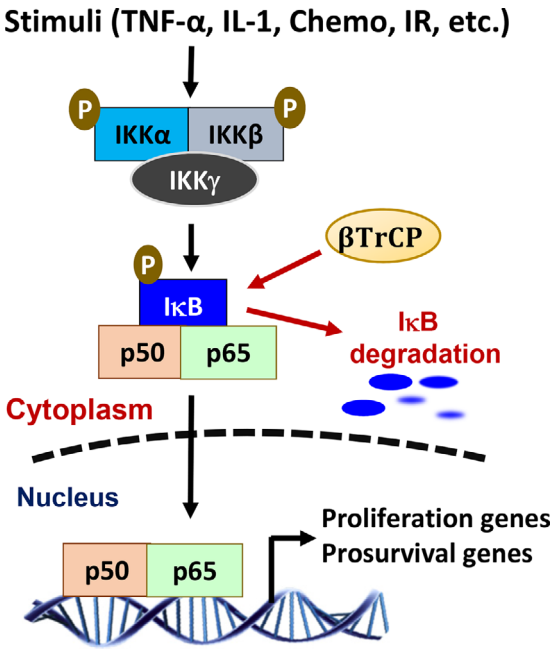

FIGURE 5 Overview of nuclear factor-κB signaling pathway. Nuclear factor-κB is naturally inhibited by IκB. Upon activation by upstream signals (e.g. tumor necrosis factor-α [TNF-α], interleukin-1 [IL-1], chemotherapy [Chemo], ionizing radiation [IR], etc.), IκB becomes phosphorylated by IκK (inhibitory κB protein [IκB] kinase), which triggers the proteasomal degradation of IκB by the $SCF^{\beta TRCP}$–ubiquitin ligase complex, which frees nuclear factor-κB to translocate into the nucleus and activates gene transcriptions, thereby promoting proliferation and survival

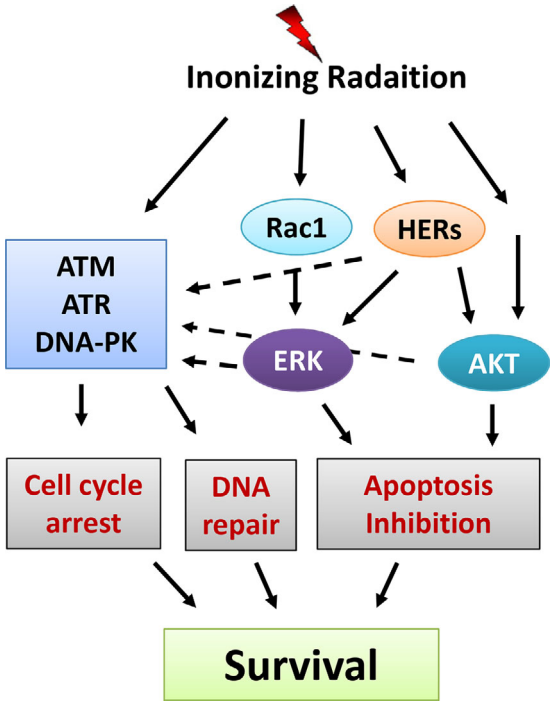

FIGURE 6 Overview of radiation-induced signaling pathways that promote cell survival. Activation of ataxia telangiectasia mutated (ATM), ataxia telangiectasia mutated and Rad3-related (ATR), and DNA-PK signaling by radiation leads to cell cycle arrest and DNA repair. Activation of human epidermal growth factor receptor (HER), extracellular signal-regulated kinase (ERK) 1/2, and protein kinase B (AKT) signaling pathways by radiation suppresses apoptosis induction. HER, ERK1/2, and AKT signaling activation after radiation positively regulate cell cycle checkpoint response and DNA repair

cycle-specific genes, such as cyclin D1, which has been associated with reinforcing radioresistance.[120]

4 | IR-ACTIVATED AUTOPHAGY SIGNALING PATHWAY

Autophagy is a lysosomal self-digestion process through which superfluous organelles, proteins, and cytosol are metabolically degraded.[123] Autophagy can be activated by a number of stimuli, including DNA damage, oxidation stress, starvation, extracellular matrix detachment, and hypoxia. Under most conditions, autophagy promotes cell survival by eliminating damaged organelles and proteins aggregates, as well as by facilitating energetic homeostasis, whereas recent studies also showed that autophagy can promote cell death.[123,124] When activated, the highly organized autophagy involves a sequence of events comprising sequestration and degradation of damaged cytosolic cargos. The autophagic signaling starts with the inhibition of the Akt/mTOR pathway, leading to the activation of Atg1, which recruits and forms a complex with Atg13 and Atg17. In parallel, other autophagy-related molecules form another complex through PI3K class 3 complex, and are recruited over a double-membrane structure to form autophagosome, which ultimately fuses with a lysosome and leads to the degradation of damaged cargos.[123,125] Radiation not only induces ROS and RNS, which cause oxidative stress in cells and impede mitochondrial function, but also induces DSBs/SSB DNA damage and activates various stress response signaling pathways involved in cell cycle checkpoint control and apoptosis, all of which have been shown to induce autophagy.[126–129] The fate of autophagy in the cellular response to radiation can be either apoptosis that removes the damaged cells or survival that can lead to radioresistance. The determinants of the fate of IR-induced autophagy are likely to be depended on multifactors, such as the type of cells, extent of IR, and nutrient condition.[130–132]

5 | CONCLUSION

Radiation therapy serves as an indispensable modality for cancer treatment, whereas radioresistance remains a major obstacle limiting the efficacy of radiation therapy. In order to solve the problem, it is necessary that we fully understand the signaling networks that protect cancer cells from radiation-induced cytotoxicity, leading to survival. As discussed above, the lethal cytotoxicity caused by IR is mainly the result of DSBs. However, radiation also concurrently induces multiple prosurvival signaling pathways that protect cancer cells from the

cytotoxic effect of radiation. Among those, AKT- and ERK1/2-activated signaling protects the irradiated cells from undergoing apoptosis induction, while signaling mediated by ATM and ATR drives cells into cycle arrest and initiates DNA repair. Furthermore, DSBs can directly activate DNA-PK signaling to initiate NHEJ-mediated DNA repair. Additionally, HER, ERK1/2, and AKT signaling also positively regulate the cell cycle checkpoint response and DNA repair machinery. Consequently, these signaling pathways act conjointly to rescue cancer cells from radiation-induced injury and promote radioresistance (Figure 6). In order to overcome radiation therapy resistance, pharmacological approaches that block these prosurvival signaling pathways are anticipated to enhance the radiosensitivity of cancer cells.

CONFLICT OF INTEREST

The authors declare no competing interests.

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