Dual effects of active ERK in cancer: A potential target for enhancing radiosensitivity (Review)

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Abstract. Ionizing radiation (IR) is an important cancer treatment approach. However, radioresistance eventually occurs, resulting in poor outcomes in patients with cancer. Radioresistance is associated with multiple signaling pathways, particularly pro-survival signaling pathways. The extracellular signal-regulated kinase 1/2 (ERK1/2) cascade is an important signaling pathway that initiates several cellular processes and is regulated by various stimuli, including IR. Although numerous studies have demonstrated the pro-survival effects of active ERK, activation of ERK has also been associated with cell death, indicating that radiosensitization may occur by ERK stimulation. In this context, the present review describes the associations between ERK signaling, cancer and IR, and discusses the association between ERK and its pro-survival function in cancer cells, including stimuli, molecular mechanisms, clinical use of inhibitors and underlying limitations. Additionally, the present review introduces the view that active ERK may induce cell death, and describes the potential factors associated with this process. This review describes the various outcomes induced by active ERK to prompt future studies to aim to enhance radiosensitivity in the treatment of cancer.

Contents

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1. Introduction

Ionizing radiation (IR) serves an essential role in modern cancer management due to its unique advantages, including non-invasiveness and a lack of intense systemic toxicity (1). As an integral component of adjuvant and palliative treatment strategies for primary and advanced/metastatic tumors, respectively, radiation therapy (RT) is administered for the management of nearly two-thirds of all types of cancer, including cancer of the prostate, cervix, bladder, head and neck, breast, lung, brain, pancreas and skin, anorectal cancer, and soft-tissue sarcomas (2). Although RT has demonstrated various degrees of success, recurrence and treatment failure may occur in patients due to intrinsic or external radioresistance (3). Therefore, strategies are urgently required for enhancing radiosensitivity in the treatment of cancer. Targeted molecular therapy has gained increasing attention for evaluating the effect of IR on targets of specific cancer-associated signaling pathways. Numerous preclinical and clinical studies have demonstrated that combination therapies using radiation and targeted molecular agents improve tumor response rates and clinical outcomes (4-6). Five potential therapy mechanisms have been described: i) Spatial cooperation; ii) temporal modulation; iii) biological cooperation; iv) cytotoxic enhancement; and v) normal tissue protection (7). Among the numerous signaling molecules, extracellular signal-regulated kinase (ERK) is one of the most important.

The ERK cascade functions as a crucial intermediary in intracellular signal transduction networks to transmit signals from extracellular stimuli, such as growth factors, hormones and neurotransmitters, among others (8). Increasing evidence indicates that activation of ERK induces cell proliferation and confers a survival advantage on cells, giving it a major role in human cancer (9). Therefore, pharmaceutical inhibitors targeting one of the common signals, the RAS/RAF/MEK/ERK signaling pathway, have been developed to improve the clinical outcomes of patients with cancer (6,10). However, even when tumors exhibit a positive primary response to these inhibitors, poor therapeutic effects may result from acquired resistance (11). Additionally, the mechanisms of resistance to ERK1/2 pathway inhibitors are unknown. Some studies have demonstrated that ERK activation leads to non-prosurvival effects in cancer cells (12-15). Particularly, active ERK may lead to cell death under different circumstances, such as location of ERK and time and extent of active ERK, which may

result in radiosensitization in human cancer (4,5). Therefore, the true effect of ERK must be clarified before combining RT and ERK inhibitors for cancer treatment. In the current review, the dual effects of activated ERK on cancer cells and their respective potential mechanisms are summarized. The ways in which active ERK induces cell survival are described, including the molecular mechanisms, clinical use and limitations. Additionally, the association between ERK activation and cell death is described, as well as the influence of ERK on the response to IR in cancer cells. The present review provides a foundation for developing cancer therapies targeting the function of ERK.

2. ERK and cancer

ERKs belong to the family of mitogen-activated protein kinases (MAPKs), which also includes ERK5, c-JunNH2-terminal kinase and p38 MAPK (15). The present review focuses on ERKs, which include two isoforms, ERK1 and ERK2 (also known as p44 and p42 MAPK, respectively). Generally, ERK activation may occur in two ways; activated-ERK is associated with the autocrine/paracrine signaling of mitogenic growth factors through tyrosine kinase receptors, such as the epidermal growth factor receptor (EGFR), the insulin-like growth factor receptor or c-MET, induced by various stimuli (16). Additionally, ERK activation may occur as a result of abnormal activation or genetic alterations in its upstream signaling molecules, such as RAS, RAF and MEK1/2 (17). The RAS/RAF/MEK/ERK cascade is the typical signaling pathway following the three-stage enzymatic cascade of MAPKs (18). In this pathway, growth and survival factors activate RAS GTPases by promoting the release of GDP to allow GTP binding. Active RAS-GTP then binds to one of the RAF protein kinases, ARAF, BRAF or CRAF (also known as MAPK3K), resulting in their activation. Subsequently, RAF phosphorylates and activates MEK1/2 (also known as MAP2K1/2), which in turn phosphorylate and activate ERK1/2 (19). Once activated, ERK1/2 can regulate ~250 potential substrates, including transcription factors, protein kinases and phosphatases, cytoskeletal elements, regulators of apoptosis and a variety of other signaling-associated molecules (20,21). Activated-ERK can lead to various physiological responses, as shown in Fig. 1 (22).

Under normal conditions, ERK signaling is regulated by feedback loops at multiple levels, which are essential for regulating cell growth and homeostasis. However, under abnormal circumstances, activated ERK may lead to various pathological changes (23), including tumorigenesis (24), diabetic nephropathy (25), viral infection (26), cardiovascular disease (27) and Alzheimer's disease (28). Nearly one-third of all types of cancer, including melanoma, uveal melanoma, and pancreatic, non-small cell lung, colorectal, basal-like breast and hepatic cancer, involve deregulated ERK (9). Hoshino *et al* (29) revealed that ERK was constitutively active in ~50 tumor cell lines (36.2%) in a tissue-specific manner; cell lines derived from the pancreas, colon, lung, ovary and kidney exhibited high frequencies of constitutive ERK activation, while those derived from the brain, esophagus, stomach and liver, and those of hematopoietic origin, exhibited low frequencies with a limited degree of ERK activation. Additionally, other stimuli, such as IR and chemotherapy drugs, can activate ERK and affect the efficacy of cancer therapy, with some exceptions (11,30). For example, Corn *et al* (31) observed that phosphorylated ERK-positive cancer cells became ERK-negative after RT in colorectal cancer. Overall, active ERK seems to be closely associated with the onset, development, invasion, metastasis and therapy-resistance of most types of tumor.

3. ERK and irradiated cancer cells

IR is known to induce cell toxicity by damaging biological molecules directly and indirectly. High-linear energy transfer (LET) radiation, such as α particles and neutrons, directly ionizes cellular macromolecules, including DNA, RNA, lipids and proteins, while low-LET radiation, such as X-rays and γ-rays, indirectly damages biological macromolecules by generating reactive oxygen species, such as superoxide and hydroxide radicals (32). Indirect DNA damage from free radicals accounts for ~65% of radiation-induced DNA damage, which is characterized by both single- and double-stranded breaks (DSBs) in DNA, with the latter being more lethal than the former (30).

IR or DNA damage are important stimuli that can activate ERK, one of the most crucial signaling pathways (33,34). Notably, IR induces phosphorylation of ERK in a time-dependent manner; activation of ERK1/2 appears as early as 15 min after IR, with maximum activation observed after 24 h (35,36). The extent of ERK activation by radiation varies. For example, intense ERK activity is typically induced by low doses of radiation (1 Gy) rather than by high doses (6 Gy) (37). Additionally, IR can induce numerous other signaling pathways within cells, including EGFR, PI3K/AKT/mTOR and cell cycle checkpoint signaling pathways (38-40). These pathways in turn activate ERK and are upstream molecules of ERK (41). For example, Sambade *et al* (42) observed that activation of ERK1/2 by EGFR typically occurred at a later phase (60 and 90 min) rather than an early phase (15 and 30 min) after radiation.

Once activated, ERK participates in cell proliferation and survival through a variety of mechanisms that affect the radiosensitivity of tumor cells. In general, activated ERK protects tumor cells from radiation-induced death in numerous ways. Park *et al* (43) determined that ionizing radiation-induced MAPK can activate the progression elevated gene 3 promoter, thereby increasing the expression levels of vascular endothelial growth factor (VEGF) protein in glioblastoma. VEGF promotes tumor angiogenesis and is associated with endothelial radiosensitization (3). Similarly, activated ERK increases RAD51 expression in pancreatic cancer cells (44), which promotes homologous DNA repair, leading to RT resistance (45). In addition, a recent study determined that γ-ray irradiation alone can increase cell migration *in vitro*, which is mainly achieved by activating the EGFR/ERK/AKT signaling pathway and increasing the expression of nuclear factor γB (NFγB) (46). After pretreatment with olaparib, a poly(ADP-ribose) polymerase inhibitor, activation of the EGFR/ERK/AKT signaling pathway induced by γ-rays was inhibited, thereby reducing the metastatic capacity of tumor cells (46). However, some studies have found that activated ERK can promote RT-induced cell death, thereby increasing radiosensitivity (47). The mechanisms involved in this process

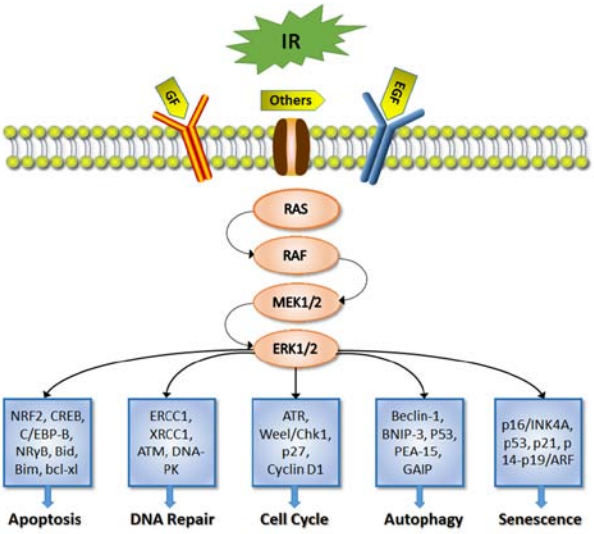

Figure 1. ERK signaling. The ERK signaling pathway can be stimulated by ionizing radiation via growth factor and EGFR. Active ERK participates in various cellular processes, such as apoptosis, DNA repair, cell cycle, autophagy and senescence. IR, ionizing radiation; GF, growth factor; EGF, epidermal GF; MEK1/2, mitogen-activated protein kinase 1/2; ERK, extracellular signal-regulated kinase 1/2; EGFR, epidermal growth factor receptor.

mainly include abrogating radiation-induced G_2/M arrest, apoptosis and autophagy (47-49). Therefore, activated ERK serves various roles in cancer cells, and the functions of activated ERK1/2 are influenced by numerous factors, including cell type, location of ERK, and time and extent of active ERK (5). The present review discusses two opposite outcomes of ERK activation: Pro-survival and pro-death.

Improvement in radiosensitivity by ERK inhibition. As aforementioned, radiation can induce rapid activation of ERK in various cancer cell types (50). A study has demonstrated that activated ERK protects cancer cells from the cytotoxic effects of radiation (51). ERKs promote cell survival in various ways, including via the inhibition of apoptosis, the induction of DNA damage repair and the arrest of the cell cycle.

Apoptosis, or programmed cell death type I, is an essential process leading to the removal of damaged cells without affecting normal cells, following DNA damage or during development (52). Apoptosis can be triggered by the caspase-mediated intrinsic signaling pathway, which is mainly regulated by the B-cell lymphoma 2 (Bcl-2) family of intracellular proteins, or by an extrinsic signaling pathway, which is closely regulated by the tumor necrosis factor (TNF) receptor family (53,54). Deregulation of apoptosis is associated with uncontrolled cell proliferation, cell growth, progression of cancer and cancer resistance to drug therapies (55,56). Therefore, apoptosis deregulation is considered a hallmark of cancer (55). Two types of proteins determine the cellular outcome: Pro-apoptotic proteins, such as Bcl-10, Bak, Bid, BAG, Bax, Blk, Bad and Bim, and anti-apoptotic proteins, such as Bcl-2, Bcl-x, Bcl-XS, Bcl-xl, Bcl-w, IAP and Mcl-1 (56). ERK activation induced by IR can activate various substrates, which transmit the signaling of ERK to apoptosis-associated proteins; common substrates include transcription factors, such as nuclear factor erythroid 2-related factor 2 (NRF2), cyclic AMP-responsive element binding protein (CREB) and CAAT/enhancer binding protein β (C/EBP-β) (57,58). Chen *et al* (57) observed that radiation-induced ERK1/2 phosphorylation increased NRF2 expression in osteosarcoma U-2 cells; activation of NRF2 served a radioprotective role by stimulating Bcl-2 and p65 expression, while inhibiting Bax and p53 expression. Similarly, ERK1/2 can induce Bcl-xl, Mcl-1 and c-FLIPs expression via CREB and C/EBP-β activated by ERK1/2 (38). Additionally, ERK is able to activate the NFγB1 dimer, a crucial regulator of anti-apoptotic genes, including genes encoding inhibitors of apoptotic proteins and members of the Bcl-2 family (59). Furthermore, ERK can directly stimulate Bid and Bim (38). Therefore, ERK1/2 is associated with apoptosis and can protect against cell death mainly by increasing or decreasing levels of anti- and pro-apoptotic proteins, respectively.

DNA damage repair is essential in the cancer cell response to IR and includes at least five main processes: Base excision repair, nucleotide excision repair, mismatch repair, homologous recombination (HR) repair and non-homologous end joining (NHEJ) (60). HR and NHEJ, the major repair pathways for DNA DSBs and closely associated with ERK (61), are mainly regulated by PI3K-like kinases, including ataxia telangiectasia mutated (ATM), RAD3-related protein (ATR) and DNA-dependent protein kinase (DNA-PK) (62). Additionally, DNA DSB repair is modulated directly or indirectly by other means, such as EGFR and the ERK axis (63). ERKs can directly activate ATM or DNA-PK, which mainly participate in NHEJ-mediated DSB repair (4). Furthermore, ERK can activate ATR followed by cell cycle arrest (22). Additionally, activation of ERK induced by IR has been associated with increased levels of transcriptional proteins (such as ERCC1 and XRCC1) involved in DNA repair in DU145 and LNCaP prostate carcinoma (64,65). However, in one study, radiation-induced ERK activation was affected by the extent or scope of DSB: Low-level DSBs (equivalent to 2 Gy) resulted in ERK activation, while high-level DSBs (>2 Gy) led to phosphatase-mediated ERK dephosphorylation and subsequent suppression of the ERK signaling pathway (4). Therefore, activation of ATM or ATR by activated ERK may depend on the radiation dose. Overall, ERK seems to be associated with DNA repair to protect against cell death.

Cell cycle arrest, which is governed by cell cycle checkpoint-associated proteins, such as cell cycle proteins (cyclins) and cyclin-dependent kinases, can maintain gene stability by blocking cell cycle progression and initiating processes to repair the detected damage (66). Some studies have demonstrated that ERK1/2 pathway activation following IR or DNA damage is critical for the activation of cell cycle checkpoints in response to radiation cytotoxicity; these studies confirmed that phosphorylation of ERK1/2 is a prerequisite for inducing ATR expression, which can activate Wee1 and checkpoint kinase 1 as key regulators of the G_2/M checkpoint (67,68). Additionally, one study indicated that expression of basal breast cancer type 1 susceptibility protein (BRCA1) tumor suppressor is necessary for IR-induced activation of ERK, followed by G_2/M arrest, in MCF-7 cells (69). Therefore, ERK is associated with key cell cycle checkpoint proteins to induce cell cycle arrest, and serves a protective role in response to radiation cytotoxicity.

Previous studies have demonstrated that ERK signaling serves a radioprotective role in cancer therapy and contributes to radioresistance (9,29,70). Therefore, inhibition of the ERK signaling pathway may provide a valuable approach to increase the radiosensitivity of cancer cells in response to IR. Various inhibitors for suppressing ERK signaling have been tested in preclinical and clinical investigations, including RAF inhibitors (vemurafenib, dabrafenib, LGX818, TAK-632, MLN2480 and PLX-4720), MEK inhibitors (trametinib, cobimetinib, MEK162, AZD6244, RO5126766, GDC-0623 and PD0325901) and ERK inhibitors (SCH772984, VTX11e and GDC-0994) (10,11,71,72). Radiation in combination with RAF and MEK inhibitors has been widely tested *in vitro* and *in vivo* for multiple types of cancer cells and various biological mechanisms (73). Estrada-Bernal *et al* (74) demonstrated that GSK212, a MEK1/2 inhibitor, downregulates several intermediates of DSB repair signaling, including BRCA1, RAD51, DNA-PK and PPM2, in irradiated pancreatic cancer cells, and suppresses DSB damage repair, particularly through HR repair pathways. Similar results were obtained by Marampon *et al* (75) using another MEK1/2 inhibitor, U0126, which reduced DNA-PK expression induced by IR. Furthermore, radiosensitization induced by a MEK inhibitor, AZD6244, was associated with a decreased cell cycle checkpoint response and increased mitotic catastrophe compared with no inhibitor present; in these *in vitro* and *in vivo* experiments, an apparent growth delay in xenografts of A549 cancer cells was observed after AZD6244 was combined with irradiation, compared with treatment by irradiation alone. Notably, the DNA repair pathway did not differ between the combined model and each treatment alone, which may be attributable to differences in molecular structure. A study observed that ERK inhibitors sensitized cancer cells to irradiation by downregulating specific molecules, such as transforming growth factor-α and TNF-α converting enzyme, which can stimulate a radioresistance mechanism by activating EGFR after inhibiting mutant RAS (76). Therefore, ERK inhibitors may increase cell death by suppressing phosphorylation of EGFR signaling pathways. Other potential mechanisms, such as ERK inhibition, can disrupt the production of c-Myc induced by IR, which can promote the onset, progression and resistance to targeted therapy in numerous types of cancer, such as prostate cancer (6,77). Active ERK-induced apoptotic effects have been confirmed by promoting pro-apoptotic and inhibiting anti-apoptotic proteins (59). The aforementioned data suggest that inhibition of ERK signaling may be an effective treatment for some types of cancer cells.

The effects of inhibitors of ERK signaling on tumor suppression are being evaluated in various clinical trial phases; however, the observed poor outcomes are the result of acquired resistance, clinical side effects, varying functional times, intensity or other unclear reasons, which are limiting their value for clinical application (78-80). The main mechanisms of acquired resistance include: i) NRAS or KRAS mutations, amplification of BRAF V600E, mutations in MEK1/2 and loss of CDKN2A, which lead to BRAF inhibitor resistance; ii) MEK mutations or BRAF amplification, which result in MEK inhibitor resistance; iii) ERK mutations, which contribute to ERK inhibitor resistance; iv) other abnormally activated or elevated levels of molecules, such as PI3K/AKT, CCND1, receptor tyrosine kinase and CRAF128; v) a decreased dependency of tumor cells on the ERK signaling pathway for growth; and vi) rebound of MEK/ERK after inhibition treatment or compensatory mechanisms (11,18,81).

Numerous studies have revealed less satisfactory outcomes regarding ERK inhibition (11,12). Therefore, the opposing functions of active ERK must be considered, particularly when evaluating whether radiosensitivity may be improved by inducing ERK activation.

Activation of ERK: A potential strategy for radiosensitization. Some studies have suggested that activation of ERK by IR or other compounds may lead to cell death; active ERK can have a pro-death or growth-arrest role in cancer cells (15,82). Dual effects are the result of the numerous mechanisms upstream and downstream of ERK. However, the association between the pro-death effect of active ERK and radiosensitivity has not been systematically evaluated in cancer cells.

Studies have identified various stimuli that can further induce cancer cell death by activating ERK, including antitumor agents, such as taxol (83), carboplatin (48), etoposide (84), doxorubicin and cisplatin (85), elements, such as cadmium (86,87) and benzo(a)pyrene (88), irradiation (89,90), naturally derived products, such as chelerythrine (91) and piperlongumine (92), and others (82,93). Additionally, constitutively activated ERK mediates cell death. In two diffuse large B-cell lymphoma (DLBCL) cell lines, CD40-sensitive DLBCL cells were induced to undergo apoptosis by CD40 ligand (CD40L) only when ERK was constitutively activated, and this effect disappeared when the MEK inhibitor U0126 inhibited ERK phosphorylation; by contrast, CD40-resistant DLBCL cells exhibited no response to CD40L due to a lack of constitutively activated ERK (82). Three main pro-death or anti-proliferative mechanisms were involved in this process, including apoptosis-induced cell death, autophagic programmed cell death and senescence (15,94,95).

As aforementioned, both constitutive and stimuli-induced ERK signaling contribute to apoptosis and are influenced by numerous factors, some of which are closely associated with IR or radiosensitivity. Lee *et al* (47) demonstrated that overexpression of protein kinase C δ (PKCδ), a PKC isoform, contributed to the expression of phosphorylated ERK; the PKCδ-ERK signaling pathway further enhanced radiation-induced apoptosis and radiosensitivity by abrogating radiation-induced G_2/M arrest. Another isoform of PKC, PKCε, also led to radiation-induced cell death by mediating ERK activation; this pro-death effect was inhibited when NIH3T3 cells were pretreated with the MEK inhibitor PD98059 (69,89). Watanabe *et al* (90) demonstrated that PD98059 significantly inhibited radiation-induced apoptosis, further leading to radioresistance, indicating that active ERK may serve a radiosensitizing role in rat cells. In terms of ERK substrates, several studies have demonstrated that activated ERK in numerous cancer cells can phosphorylate p53, an essential tumor suppressor that serves a pivotal role in protecting genome integrity and mediating cell death (96-98), and is key to the radiation response in tumor cells. Functional p53 regulates irradiated cancer cell death by inducing apoptosis or senescence, and by inhibiting autophagy-associated cell survival (30,49,99). Pseudo-ginsenoside-Rh2, which is a

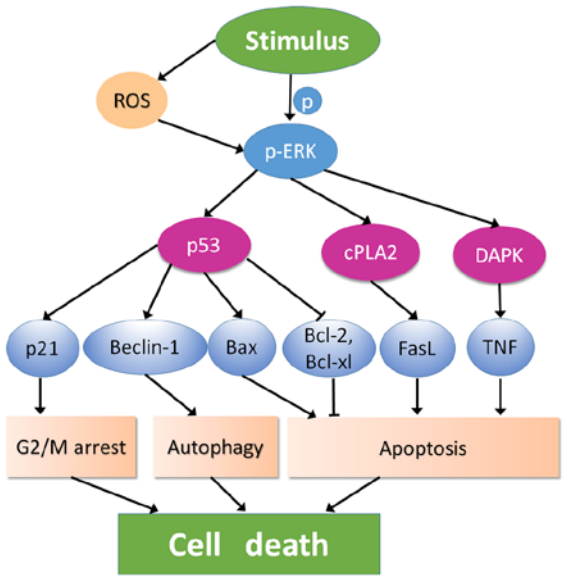

Figure 2. Mechanisms of ERK-induced cell death. Stimulus activate ERK directly or indirectly. p-ERK could induce cell death dependent of p53 or independent of p53. ROS, reactive oxygen species; p-ERK, phosphorylated extracellular signal-regulated kinase; DAPK, death-associated protein kinase; cPLA2, cytosolic phospholipase A2; TNF, tumor necrosis factor; FasL, Fas ligand; Bcl, B-cell lymphoma.

derivative of ginsenoside Rh2, has been shown to suppress cell growth and induce intrinsic apoptotic pathways through activation of the Ras/Raf/ERK/p53 signaling pathway, subsequently upregulating Bax expression and downregulating Bcl-2 and Bcl-xl expression (100). Furthermore, excessive activation of the Ras/Raf/ERK/p53-p21 signaling pathway was shown to induce apoptosis and G_2/M arrest in human lung carcinoma cells (101). A study demonstrated that activation of ERK/p53/Beclin-1 could mediated autophagic cell death in A549 cells (102). Therefore, p53 upregulation seems to be an essential mechanism of ERK-induced cell death (Fig. 2). However, other studies have suggested that ERK induces cell death independently of p53 such as cPLA2-FasL and DAPK-TNF pathway (83,103).

In addition, there are a number of other factors for which the intensity and localization of ERK activation may be key in the choice between cell survival or cell death (104). Tang *et al* (84) demonstrated that etoposide and IR resulted in DNA damage that activated ERK with the same intensity; however, low-intensity DNA damage resulted in cell cycle arrest, while high-intensity DNA damage caused apoptosis. Inactive ERK localizes in the cytoplasm, while activated ERK1/2 typically exerts its role by entering the nucleus and phosphorylating transcription factors (105). However, some studies have suggested that active ERK1/2 can access specific substrates and affect cell conditions by translocating to other organelles, such as the mitochondria (106), the endoplasmic reticulum (107) and various membranes (108). Studies have demonstrated that nuclear ERK mainly improves cell proliferation or oncogenic transformation and migration in various types of cancer either by inducing oncogenic signals, such as c-Myc or c-Fos, or by inhibiting tumor suppressors such as Tob or Foxo3a (109-112). However, stimulation of mitochondrial ERK is involved in both cell survival and apoptosis (105). For example, Cook *et al* (106) demonstrated that activation of the mitochondrial ERK1/2 signaling pathway promoted mitochondrial fission or fragmentation, with the latter being involved in the onset of cell apoptosis. A previous review stated that the specific mechanisms of the aforementioned translocation are mediated by a number of anchoring and scaffold proteins (105).

Overall, the aforementioned data suggest that activating, rather than inhibiting, ERK may increase cancer cell death. Therefore, an activator of ERK, honokiol, has been tested *in vitro* and *in vivo*. Honokiol exhibits the potential to treat cancer by inhibiting cell growth and migration by inducing ERK-dependent apoptosis and autophagy (113,114). Therefore, ERK-induced cell death may be a potential therapeutic strategy that requires further evaluation.

4. Conclusions and perspectives

RT is an indispensable tumor treatment; however, its effectiveness is limited by radioresistance. Radiobiology has revealed that increasing the radiation dose improves local tumor control, but also causes unavoidable damage to normal organs at higher doses. Therefore, the identification of novel RT strategies, such as changing the segmentation method and increasing radiosensitivity, is required to improve RT efficiency. At present, ERK is a promising target for enhancing the radiosensitivity of tumors, which are dependent on the survival-promoting role of ERK activation; however, there are numerous challenges and limitations that require further evaluation to improve clinical treatment. Since ERK activation has dual roles, the exact function of ERK should be clarified and the potential mechanisms elucidated, such as the intracellular localization of ERK and the corresponding microenvironment, before combining RT with ERK inhibitors. A number of studies have indicated that ERK activation serves a role in promoting cell death associated with the degree and duration of activation. The main role served by ERK at different doses and treatment times for different current RT regimens, such as stereotactic body and conventional RT, should be further investigated. Combining RT with targeted molecular therapy and chemotherapy may markedly enhance the therapeutic window for RT use. Clarification of the individual and comprehensive effects of treatment measures on the direction of ERK function is required before implementation of combined treatment. Therefore, in order to develop an effective treatment plan for patients with tumors by targeting the ERK signaling pathway, it is crucial to understand the mechanism of action and characteristics of combined therapy on ERK function.

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Authors' contributions

GC and BL conceived the review. YLu and BL wrote the review. YLu and XY revised the review. YLi proofread the manuscript and revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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