Review Article

Research progress on factors affecting the sensitivity of breast cancer to radiotherapy: a narrative review

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Background and Objective: Radiation therapy (RT) is one of the important components of comprehensive treatment for breast cancer and has important value in improving the control rate of local areas, reducing the chance of recurrence and metastasis after breast cancer surgery, delaying disease progression, and improving the survival of breast cancer patients. The factors that affect the RT sensitivity of breast cancer are important. The above potential predictors of radiation efficacy can provide patients with a predictive method and therefore have significant value in clinical therapy. In this paper, we have summarised the predictive factors of radiotherapy sensitivity by reviewing recent research on breast cancer and focused on the following areas: tumor immune microenvironment (TIME), cancer stem cells, noncoding RNAs, signal transduction pathways, genes, etc. This review aims to provide theoretical basis and reference for improving the efficacy of radiotherapy and experimental individualized treatment of breast cancer.

Methods: We searched the Web of Science database to identify clinical studies published between 2010 and January 2024 that investigated radiotherapy sensitivity. The main findings of the validated studies were summarised.

Key Content and Findings: Improving the radiosensitivity of breast cancer is essential in the treatment of breast cancer. The radiosensitivity can be improved by modulating immune cells or immunomodulatory factors in the TIME, modulating signal transduction pathways, and other innovative combination therapy strategies. And we also summarized the predictive markers of breast cancer radiosensitivity.

Conclusions: In this paper, we reviewed the literature and summarized the newest research advances on the radiosensitivity of breast cancer patients. This review paper includes the following six aspects: the immune microenvironment, tumor stem cells, signaling pathways, regulation of gene/protein expression, small molecule drugs, and predictive markers for radiosensitivity.

Keywords: Radiosensitivity; breast cancer; tumor immune microenvironment (TIME); cancer stem cells (CSCs); predictive markers

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Introduction

Radiation therapy (RT) plays an important role in breast cancer treatment. RT increases local control of breast cancer, reduces local recurrence of the tumor, improves long-term survival time, and reduces the mortality of patients with breast cancer (1). After breast-conserving surgery for breast cancer patients, mastectomy for breast cancer, breast reconstruction, and inoperable or resectable locally advanced breast cancer, radiotherapy can improve local-regional control and reduce the chance of recurrence and metastasis. The breast cancer can also contain some special types, such as occult breast cancer and paraneoplastic breast cancer. Radiotherapy can play an important role in decreasing the rate of lymph node recurrence and distant metastasis for breast cancer, including local or regional lymph nodes, isolated axillary lymph nodes, supra/inferior clavicular lymph nodes, and internal breast lymph nodes. For oligometastases, such as bone, brain, lung, liver, and lymph nodes, radiotherapy can relieve tumor pain and uncomfortable symptoms, control disease progression, and prolong the survival time of patients.

In recent years, radiation oncologists have studied the factors of radiotherapy sensitivity and predictive biomarkers of radiotherapy efficacy, identifying and selecting breast cancer patients who may benefit from radiotherapy (2,3). In this paper, we have summarized the potential factors of radiotherapy sensitivity for breast cancer, and this review includes five sections, including related genes, noncoding RNA, signal transduction pathways, tumor immune microenvironment (TIME), and breast cancer stem cells (BCSCs). We present this article in accordance with the Narrative Review reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-71/rc).

Methods

The following search terms were used to search the Web of Science database: “breast cancer” and “radiosensitivity” and “marker”. Articles published in English between 1 January 2010 and 1 January 2024 with these terms were searched. The research selection process was divided into the following three stages: title review, abstract review and full-text review. Original articles and review articles appropriate to the topic of this review were included in the full-text review phase. The search strategy is detailed in *Table 1*.

The TIME affects radiotherapy sensitivity of breast cancer

RT modulates the infiltration of immune cells and the expression of regulatory factors in the tumor microenvironment (TME) to improve the sensitivity of breast cancer cells to RT. A previous study (4) has shown a positive correlation between tumor infiltrating lymphocytes (TILs) in the TME and prognosis of breast cancer patients. In a retrospective study (5), some scholars examined the function of macrophage phenotypes (defined by CD163 expression) in the TME and showed that CD163-expressing macrophage led to tumor radioresistance and shortened disease-free survival after RT, which was associated with advanced stage and poor prognosis of breast cancer. Tullberg and colleagues found that (6) the relationship between TILs and the efficacy of adjuvant radiotherapy for primary breast tumors. They studied the $CD8^+$ T lymphocytes and regulatory T cells (Tregs) of postoperative tumor tissues in the TME. The results showed that patients with fewer Tregs had the greatest benefit from RT, and breast cancer patients with more $CD8^+$ T cells might benefit from radiotherapy of breast cancer. A previous study found that radiotherapy can increase the infiltration of Batf3-dependent conventional type 1 dendritic cells (cDC1s), which are driven by interferon type I (IFN-I), and promote the antitumor immunity of $CD8^+$ T cells. The above process may be downregulated in breast cancer with poor immunogenicity (7). Therefore, new ways to promote cDC1 infiltration induced by radiotherapy were studied and explored. In that study (7), they found that RT can increase the expression of the enzymes CD38 and CD73 and the content of adenosine in mice and human breast cancer cells. Their preclinical data suggested that CD73 can decrease the response to radiotherapy. CD73 blockade combined with radiotherapy may promote cDC1 recruitment to tumors and induce a systemic antitumor response, and the combination therapy of CTLA-4 blockade and RT can synergistically inhibit the growth of distant tumors. Chen *et al.* (8) used aqueous solvent diffusion method to prepare self-assembled telmisartan nanoparticles (Tel NPs) to improve the water solubility of Tel, and then, to achieve long circulation and tumor targeting *in vivo*, erythrocyte membrane (ECM) obtained by hypotonic lysis was coated on the surface of Tel NPs (ECM/Tel). Their results showed that ECM/Tel inhibited the proliferation and activation of

Table 1 The search strategy summary

Items	Specification
Date of search	01/01/2024
Databases and other sources searched	Web of Science
Search terms used	"breast cancer" and "radiosensitivity" and "marker"
Timeframe	From 1/1/2010 to 01/01/2024
Inclusion and exclusion criteria	Inclusion: the search was limited to articles published in English. The research selection process was divided into the following three stages: title review, abstract review, and full-text review. Original articles and review articles appropriate to the topic of this review were included in the full-text review phase
	Exclusion: articles not published in English and not related to the research topic were excluded
Selection process	Q.Z. conducted the article selection independently. N.L. supervised the article selection

tumor-associated fibroblasts (TAFs) and played a superior role in radiosensitization.

The TIME includes immunomodulatory factors of infiltrating immune cells, plays a crucial role in influencing the sensitivity of breast cancer cells to radiotherapy. The referenced literatures indicated that radiotherapy not only directly targeted tumor cells but also modulated the activity of immune cells within the TIME, such as TILs, macrophages, and dendritic cells (DCs), thereby impacting the efficacy of breast cancer treatment. Research had also shown that targeting immune cells within the TIME, such as blocking CD73 or combining immune checkpoint inhibitors like CTLA-4 inhibitors with radiotherapy, can enhance radiosensitivity and improve breast cancer treatment outcomes. Additionally, recent studies have explored the use of nanotechnology to enhance drug targeting and bioavailability. In future research, optimizing the combination of radiotherapy with immune modulators or nanomedicines could further improve treatment outcomes for breast cancer patients, offering new avenues for targeted cancer therapy.

Remodeling the TIME to improve breast cancer radiotherapy sensitivity

Some small molecule drugs can modulate the TIME of breast cancer by regulating immune cells and immune factors. Song *et al.* (9) found that the use of trastuzumab before fractionated radiotherapy synergistically improved the efficacy of RT *in vitro* and *in vivo* for human epidermal growth factor receptor 2 (HER2)-positive breast cancer, which was independent of anti-HER2 response alone. They found that the combination therapy modulated the TIME by increasing tumor oxygenation and decreasing the DNA damage response. A study (9) found that the combination of RT and the resveratrol analog HS-1793 can reduce DNA damage in lymphocytes, significantly increase IFN-γ^+/CD8$^+$ T-cell proliferation, reduce the secretion of TGF-β and IL-10, reduce the proportion of Treg cells, and inhibit the infiltration of tumor-associated macrophages (TAMs) in the TME. Xu and his colleagues (10) investigated and explored 1400W dihydrochloride, a potent small molecule inhibitor of inducible nitric oxide synthase (iNOS). *In-vitro* experiments showed that iNOS blockade counteracted the inhibitory effect of myeloid cells on T-cell proliferation. *In-vivo* assays showed that the combination therapy of iNOS inhibition and RT can lead to a significant increase in infiltrating CD8$^+$ T cells in the tumor and splenic tissues and upregulate serum IFN-γ and IL-2 levels. The above results suggested that the combination therapy of RT and 1400W has synergistic antitumor effects, and iNOS may be an important regulator of the antitumor immune response induced by RT. A previous study has explained that matrix metalloproteinases (MMPs) can promote tumor progression (11). In that study (12), DX-2400, a highly selective MMP14 inhibitory antibody, was investigated, and the results showed that MMP14 blockade decreased the level of TGF-β and increased the polarization of M1-type macrophages, induced an increase in iNOS in tumors, and improved vascular function and tumor tissue oxygenation.

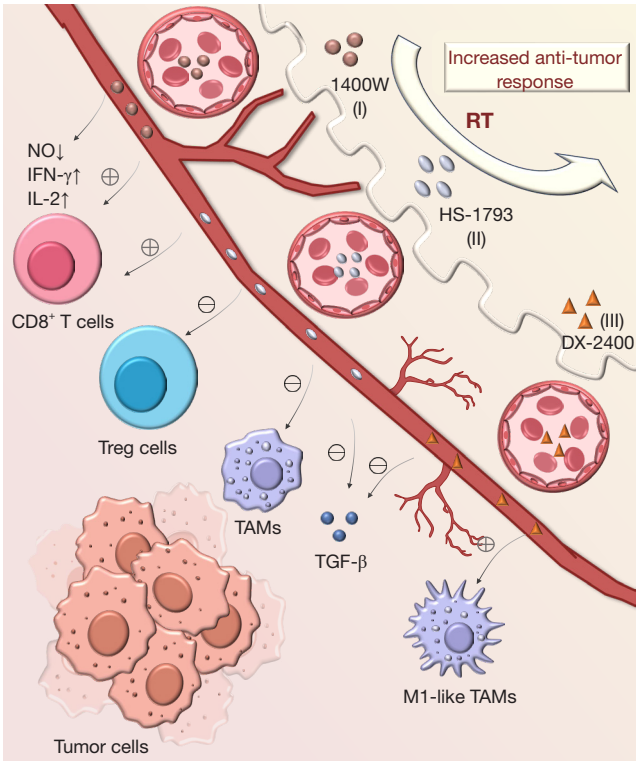

Figure 1 Different drugs combined with radiotherapy modulated the TIME. (I) 1400W, a small molecule inhibitor of iNOS, can significantly increase $CD8^+$ T cells in the TIME and upregulate the levels of IFN-γ and IL-2 in serum. (II) HS-1793 can increase the subpopulation of $CD8^+$ T cells, reduce the infiltration of Tregs and TAMs, decrease the secretion of TGF-β, and upregulate the radiosensitivity of breast cancer cells by the combination of HS-1793 and radiotherapy. (III) DX-2400, a highly selective MMP inhibitory antibody, can decrease the level of TGF-β, increase the subpopulation of M1-type macrophages, and thereby enhance radiosensitivity to breast cancer cells. RT, radiation therapy; NO, nitric oxide; IFN, interferon; IL, interleukin; Tregs, regulatory T cells; TAMs, tumor-associated macrophages; TGF-β, transforming growth factor beta; TIME, tumor immune microenvironment; iNOS, inducible nitric oxide synthase; MMP, matrix metalloproteinase.

The above process can enhance the response to RT and reduce primary tumor growth, especially in tumors with high expression of MMP14 (*Figure 1*).

It was shown that M2 macrophage polarization was mediated by STAT6 signaling (13). Subsequently, several authors (14) showed that the phosphorylated STAT6 inhibitor PM37, blocked the polarization of M2 macrophages, and downregulated the expression of protein kinase C zeta (PRKCZ), which can prevent radioresistance in inflammatory breast cancer (IBC) cells. 2-Hexyl-4-pentanoic acid (HPTA), which is a valproic acid (VPA) derivative, can function as a histone deacetylase inhibitor, and HPTA can decrease the activity of DNA repair proteins and increase the apoptosis of breast cancer cells (15). Duan and his partners (16) observed significant growth inhibition of unirradiated tumors when the tumor region was irradiated, suggesting that HPTA can stimulate RT-induced distant effects. Their results suggested that HPTA can promote myeloid-derived TAM infiltration in distant and unirradiated tumors and that HPTA can enhance the infiltration of reprogrammed TAMs. HPTA and RT can reverse the rate of the macrophage M2/M1 phenotype, inhibit tumor angiogenesis, promote vascular normalization of unirradiated tumors, and inhibit the growth of distant tumors. Similarly, a study (17) has shown that ionizing radiation (IR) combined with VPA can promote the infiltration of activated $CD8^+$ T cells in unirradiated tumors, and activated $CD8^+$ T cells can release granzyme B and induce the apoptosis of tumor cells. In addition, the combination treatment induced macrophage recruitment and polarization of the M1 phenotype, increased the levels of IL-1β and IL-12, decreased the levels of IL-10 and TGF-β, and enhanced $CD8^+$ T-cell activity and the antitumor immune response (17). Additionally, Cai and collaborators (18) found that HPTA combined with RT can activate the reprogramming of macrophages and the polarization of the M1 phenotype in TAMs, subsequently increasing IL-12 secretion and activating $CD8^+$ T cells. Autotaxin (ATX) is a secreted lysophospholipase D-like enzyme. ATX can stimulate the growth and metastasis of tumors and reduce the efficacy of antitumor therapy. An experiment (19) found that inhibition of ATX enhanced the inhibition of proliferation in cancer cells by RT, and increased apoptosis in tumors, and these results suggested that inhibition of ATX may improve the efficacy of RT for breast cancer (*Figure 2*).

There are other novel strategies to improve radiosensitivity by remodeling the tumour immune microenvironment. Hartmann and collaborators (20) established bilateral HER2-positive breast cancer mice models, they applied radioimmunotherapy with carbon ions plus CTLA-4 inhibition to selectively irradiate the original tumor. Then, they performed comprehensive single-cell RNA sequencing analysis on individual immune cell subsets in carbon ion-irradiated tumors, and compared them with immune cell infiltration in non-irradiated distant tumors.

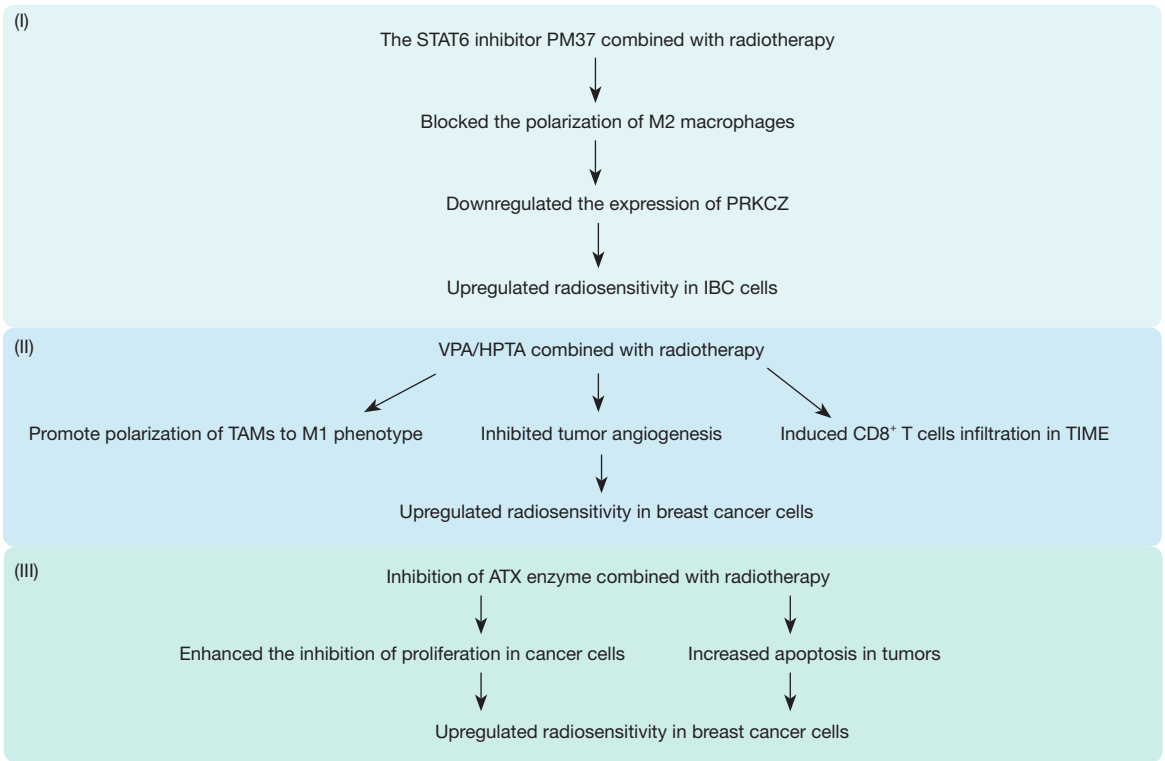

Figure 2 The process of combination therapy to improve the radiosensitivity in breast cancer. (I) The STAT6 signaling pathway mediated the polarization of M2 macrophages. The phosphorylated STAT6 inhibitor PM37 blocked M2 macrophage polarisation, downregulated the expression of PRKCZ and upregulated radiosensitivity in IBC cells. (II) VPA/HPTA combined with radiotherapy treatment promoted the polarization of M1 phenotype, promoted the infiltration of activated $CD8^+$ T cells into TIME, and inhibited tumor angiogenesis and tumor growth. (III) Inhibition of the ATX enzyme combined with RT inhibited the proliferation of cancer cells, and increased apoptosis in tumor cells, subsequently, improved the radiosensitivity of breast cancer cells. IBC, inflammatory breast cancer; VPA, valproic acid; HPTA, 2-hexyl-4-pentanoic acid; TAMs, tumor-associated macrophages; TIME, tumor immune microenvironment; ATX, autotaxin; PRKCZ, protein kinase C zeta; RT, radiation therapy.

They observed that direct irradiation induced conversion of the intratumoral myeloid compartment and accumulation of natural killer cells in the TIME, and the unirradiated TIME showed an increase in activated $CD8^+$ T cells. They showed that radioimmunotherapy with carbon ion plus CTLA-4 blockade reshaped the composition of tumor-infiltrating immune cells and could even induce complete rejection of unirradiated tumors. Yang and colleagues (21) also established bilateral tumor mice models of breast cancer cells, their experiments explored the induction of anti-tumour immune responses by Bacillus Calmette-Guérin (BCG) in combination with hypofractionated radiotherapy (H-RT). They observed that the combination therapy could remodel the immune microenvironment by increasing the infiltration of $CD8^+$ T cells, promoting the maturation of DCs, decreasing the infiltration of immune-suppressing cells, and downregulating immune-suppressing cytokine expression in a way to remodel the immune microenvironment and alleviate leukocyte-like responses. Thus, they showed that this combination therapy could enhance the systemic anti-tumor response and reduce the systemic tumor burden by remodeling the TIME. Tian and colleagues (22) have discovered a novel strategy to enhance radiotherapy efficacy based on a metal-phenol network nanoplatform. The first step was to alleviate the tumor hypoxia in TIME by noninvasive controlled low-intensity pulsed ultrasound (LIPUS). In the second step, based on the use of poly-ethylene glycol (PEG) polymer, the PEG-polyphenols encapsulated radiosensitizer platinum (Pt), and assembled with sonosensitizer PEG-purpurin 18 (PEG-P18), PP18-Pt NPs were synthesized. Then, PP18-Pt NPs were injected intravenously into 4T1 tumor-bearing

mice. Finally, RT combination with sonodynamic therapy produced high concentrations of reactive oxygen species (ROS), activated the body's antitumor immune response, and inhibited the growth of breast cancer cells. Zou and colleagues (23) developed a multifunctional nanoplatform PCN-224@IrNCs/D-Arg (PID), the nanoplatform PID combined with RT can operate as an immunomodulator to reverse immunosuppressive TIME, stimulate DC cells maturation, and fully activate anti-tumour immunity by repolarising M2 macrophages to M1 phenotype, then, ultimately amplify the efficacy of the radiation and lead to higher immunogenic cell death (ICD). They found that combination therapy improved the radiosensitivity of breast cancer. Chen *et al.* (24) designed a UiO-66-NH2@AuNS core-shell structure, then the UiO-66-NH2 core was etched by $NaHCO_3$ to offer a hollow gold nanoshell (HAuNS). This was followed by surface functionalization with biotin-PEG-SH (PEG-bio) to obtain HAuNS@PEG-bio as a therapeutic platform. The HAuNS@PEG-bio demonstrated effective photothermal therapy (PTT) function near-infrared II (NIR-II) region, where temperature increased at the tumor site promoted blood circulation and alleviated hypoxia in the TIME. Meanwhile, elemental aurum had a significant effect on radiosensitization. They found that combination treatment in mouse models of breast cancer further enhanced the radiosensitivity, initiated ICD, activated the immune response, and improved treatment efficacy. Huang and colleagues (25) introduced a gas diffusion method to synthesize Te-driven maple leaf shaped manganese carbonate nanotherapeutics ($MnCO_3$@Te), and also provided a catalytic strategy *in situ* to remodel the TIME and enhance the ROS level for improving cancer radioimmunotherapy. The results showed that $MnCO_3$@Te synergized with RT and immune checkpoint blockade therapy effectively inhibited breast cancer growth and lung metastasis *in vivo*. Overall, these findings suggested that $MnCO_3$@Te successfully overcame radioresistance and activated the immune systems, which showed promising potential in radioimmunotherapy for breast cancer. Huang and his colleagues (26) developed a new adeno-associated virus (meAAV) neoantigen vaccine, and they combined the vaccine and radiotherapy in mouse models of breast cancer. They observed that the combination therapy significantly enhanced neoantigen-specific cytotoxic T-lymphocyte (CTL) responses, increased the CTL infiltration in the TIME, reduced tumor-associated immunosuppression, and ultimately reduced tumor growth of breast cancer in tumor-bearing mice. Hu *et al.* (27) developed tumor cell-derived microparticles loaded with paclitaxel (MP-PTX), which can deliver drugs by targeting tumor cells. They combined MP-PTX with RT and applied to triple-negative breast cancer (TNBC) mouse models, and the results of *in-vitro* and *in-vivo* studies showed that the combined treatment could significantly inhibit tumor cell proliferation, enhance the killing effect on tumor cells, effectively alleviate the immunosuppressive TIME and activate the anti-tumor immune response, which provided a preferable option for the clinical treatment of refractory tumors such as TNBC. We have summarized the above combined treatment methods in *Table 2*.

Combined with the above literatures, these studies demonstrated multiple strategies to remodel the TIME, such as radiotherapy combined with trastuzumab, radiotherapy combined with some small molecule inhibitors, etc., to modulate the function of immune cells by upregulating or downregulating the expression of some relevant cytokines or signaling pathways, and to upregulate the radiosensitivity of breast cancer cells by remodeling the TIME.

In the field of breast cancer treatment, innovative combination therapy strategies continue to push the boundaries between conventional radiotherapy and immunotherapy. These strategies improve the efficiency of radiotherapy and activate the body's immune response by finely tuning the TIME, such as some recent studies that can effectively remodel the TIME through carbon ion radioimmunotherapy in combination with CTLA-4 blockers and the use of nano-platforms such as metallaphenol networks, multifunctional nanoparticles, etc., as well as new types of immunotherapy (e.g., vaccines). In summary, the above studies highlight the ability to dramatically improve breast cancer outcomes through innovative combination therapy strategies, especially combining radiotherapy, immunomodulators, and nanotechnology. Future research should focus on optimizing the clinical application of these therapeutic strategies, addressing potential safety concerns, and further enhancing treatment through precision medicine.

The relationship between BCSCs and RT sensitivity

There are many important enzymes in the biological metabolic process, which in turn affect the radiosensitivity of breast cancer cells by regulating the activity of the enzymes. Dopamine beta-hydroxylase (DBH), a specific

Table 2 Combination therapy can reshape the tumour immune microenvironment to improve radiotherapy efficacy

Combined treatment methods	Effects	Reference
CTLA-4 blockade combination with carbon ion irradiation	Reshaped the composition of tumor-infiltrating immune cells	Hartmann *et al.* (20)
BCG combination with H-RT	Enhanced the systemic anti-tumour response	Yang *et al.* (21)
LIPUS and PP18-Pt NPs combination with RT	Alleviated the tumor hypoxia and activated the body's anti-tumor immune response	Tian *et al.* (22)
Nanoplatform PID combined with RT	Led to higher immunogenic cell death	Zou *et al.* (23)
HAuNS@PEG-bio combined with RT	Alleviated hypoxia and further enhanced the radiosensitivity	Chen *et al.* (24)
$MnCO_3$@Te and immune checkpoint blockade combined with RT	Inhibited the breast cancer growth and lung metastasis	Huang *et al.* (25)
MeAAV combined with RT	Increased the CTL infiltration in the TIME, reduced tumour-associated immunosuppression	Huang *et al.* (26)
MP-PTX combined with RT	Inhibited tumor cell proliferation and activated the anti-tumour immune response	Hu *et al.* (27)

BCG, Bacillus Calmette-Guérin; H-RT, hypofractionated radiotherapy; LIPUS, low-intensity pulsed ultrasound; PP18-Pt, PEG-purpurin 18-platinum; PEG, poly-ethylene glycol; NPs, nanoparticles; RT, radiation therapy; PID, PCN-224@IrNCs/D-Arg; HAuNS, hollow gold nanoshell; PEG-bio, biotin-PEG-SH; meAAV, adeno-associated virus neoantigen vaccine; MP-PTX, microparticles loaded with paclitaxel; CTL, cytotoxic T-lymphocyte; TIME, tumor immune microenvironment.

inhibitor of the activated checkpoint kinases CHK1 and CHK2 (CHK1/2), inhibited the CHK1/2 signaling pathway, which can significantly reduce DNA damage in irradiated cells. Radiation treatment also enhanced DNA repair in a dose- and time-dependent manner by modulating the percentage of BCSCs, which express the marker $CD44^+/CD24^-$, decreasing the number of BCSCs and thus enhancing the effect of radiotherapy (28). Zhang and colleagues (29) found that the activity of M2 isoform pyruvate kinase (PK-M2) was inhibited by radiation-induced oxidative stress, and a PK-M2 activator depleted BCSCs *in vitro* through metabolic processes. The combination of a PK-M2 activator and radiotherapy can enhance the radiotherapy efficacy for drug-resistant breast cancers, including TNBC. Diacylglycerol acyltransferase 2 (DGAT2) enzyme was required for lipid droplets (LDs) biogenesis process. The results showed that DGAT2 inhibitors, PF-06424439 decreased the expression of several lipid-related genes and the LDs number, reduced the epithelial-to-mesenchymal transition (EMT) phenotype, decreased the migration ability of cancer cells, and enhanced the radiosensitivity of MCF7 cells. They suggested that radiosensitivity could be improved by the combined treatment of DGAT2 enzyme and RT (30). There are also many important proteins that, by regulating their expression, in turn, affect the radiosensitivity of breast cancer cells. Musashi RNA binding protein is an important stemness-related regulator. Troschel and colleagues (31) demonstrated that the knockdown of Musashi RNA binding protein can downregulate the expression of BCSC markers by downregulating the Notch pathway. Subsequently, the cancer cell cycle was altered. The proliferation of breast cancer cells was inhibited, and the apoptosis of breast cancer cells was upregulated. Haiduk *et al.* (32) also found that both MSI1 and MSI2 proteins were overexpressed in IBC. MSI knockdown reduced proliferation and cancer stem cell (CSC) features while increasing apoptosis. These results showed that breast cancer cells acquired enhanced radiosensitivity. RAD51-associated protein 1 (RAD51AP1) is a protein related to the homologous recombination pathway (33). Group (34) observed increased expression of the *RAD51AP1* gene in both ductal estrogen receptor-positive (ER^+) and basal TNBC. They also found that the knockdown of *RAD51AP1* can reduce the self-renewal of BCSCs and enhance the response of breast cancer cells to radiotherapy (35). TGF-β plays a key role in radiation-induced resistance and multiple processes in cancer cells, such as proliferation, angiogenesis, EMT, and metastasis, which may affect radiation efficiency. Yadav and colleagues (36) found that radiation-induced resistance in breast cancer cells was mediated through TGF-β signaling, which may lead to the EMT process and an increase in CSCs. TGF-β signaling may be an important

pathway to eliminate metastasis and radioresistance and improve the survival time of breast cancer patients. A previous study (37) found that the overexpression of the GDF15 protein in breast cancer cells, which belongs to the TGF-β superfamily, might reduce the radiosensitivity of breast cancer cells *in vivo*, inhibit the death of radiation-induced cancer cells, and promote the growth of breast cancer cells by suppressing TGF-β1-associated cytotoxic effects. In another study, Zhao and coworkers (38) reported that breast cancer cells with acquired radioresistance can exhibit high expression of the GDF15 protein, and the GDF15 protein enhanced the EMT process and stem cell-like features of breast cancer cells. The formation of mammospheres and an increased proportion of $CD44^+/CD24^-$ stem cells were subsequently observed. Furthermore, the downregulation of GDF15 protein expression sensitized radioresistant cells and significantly inhibited the EMT process and stem-like properties. Vactosertib is an oral and bioavailable TGF-β type I receptor inhibitor, and research (39) found that the combination of vactosertib and RT can inhibit the radiation-induced EMT process, CSC properties, radiotherapy-related ROS stress, and tumor metastasis. They concluded that the combination therapy of vactosertib and RT had great potential for the clinical application of breast cancer.

There were other groups that have found studies of BCSCs and radiosensitivity. There was an experimental study (40) related to the DNA minor groove binding ligand DB(n) series of synthetic dimeric bisbenzimidazoles. The study found that the combination of DB compounds and radiation can augment the damage of γ-rays on CSCs, inhibit the radiation-induced EMT process, and increase their radiosensitivity. A further study (41) evaluated the anticancer effects of the benzimidazole derivative methylimidazole (MBZ) on TNBC. They treated several types of breast cancer cells with MBZ, including radiation-resistant breast cancer cells, and the results showed that MBZ can effectively induce the arrest of the cancer cell cycle and DNA damage and downregulate the protein expression of CD44 and OCT3/4 in CSCs, as well as endothelial cell-specific molecule-1. They concluded that MBZ may be an effective anticancer medicine that can overcome the radiation-induced resistance of TNBC. A working group (42) studied the effect of Maprang seed extract (MPSE) on breast cancer cells and found that pretreatment with MPSE cultured with breast cancer cells *in vitro* can enhance radiation-induced DNA damage and tumor cell death. By targeting the PI3K/Akt and MAPK pathways in breast cancer cells, MPSE can attenuate the radiation-induced EMT process and reduce the expression of the tumor stemness phenotype and the formation of mammospheres. Their findings described a novel strategy to improve the efficacy of RT with a safe, low-cost and natural product, MPSE (*Figure 3*).

In an experiment (43), a mesenchymal stem cell (MSC)-conditioned medium suppressed the Stat3 signaling pathway, inhibited breast cancer growth, reduced the population of ALDH-positive breast cancer CSCs, and reduced the migration and metastasis of breast cancer. A previous study (44) has shown that gold nanoparticles (GNPs) can absorb X-rays and lead to a dose-enhancing effect of radiation. Recent evidence (45) suggested that MSCs can specifically accumulate in cancer tissue and human MSCs were delivered with GNP carriers as a targeted delivery system to enhance the effect of RT on transplanted tumor mice with breast cancer cells (46). Yang *et al.* (47) first proposed a method that can target breast CSCs by combining curcumin with glucose nanogold particles (Glu-GNPs). They found that the combination therapy of curcumin and Glu-GNPs may induce elevated ROS levels in breast cancer, inhibit the expression of HIF-1a and heat shock protein 90 (HSP90) protein, and promote the apoptosis of CSCs under hypoxic conditions. The results showed that this combination therapy may improve the radiosensitivity of BCSCs.

The above literature mentions a variety of strategies for targeting BCSCs. First, some studies have focused on the regulation of enzymes and proteins associated with stem cells. For example, by inhibiting the CHK1/2 signaling pathway and PK-M2 activity, the number of BCSCs can be reduced and the efficacy of radiotherapy can be improved. Secondly, some compounds may work by inhibiting the EMT process or reducing the expression of stem cell markers. In addition, the use of nanotechnology, such as GNPs and glucose nanogold particles, has been investigated for targeting BCSCs. These nanoparticles can have enhanced effects in RT by affecting the behavior of BCSCs by inducing elevated levels of ROS or inhibiting the expression of specific proteins, thereby enhancing their radiosensitivity. The combined application of these strategies may provide new directions and opportunities to improve breast cancer radiosensitization.

Radiotherapy-sensitive associated noncoding RNA

One study (48) showed that miR-200c sensitized breast cancer cells to irradiation by targeting UBQLN1 and

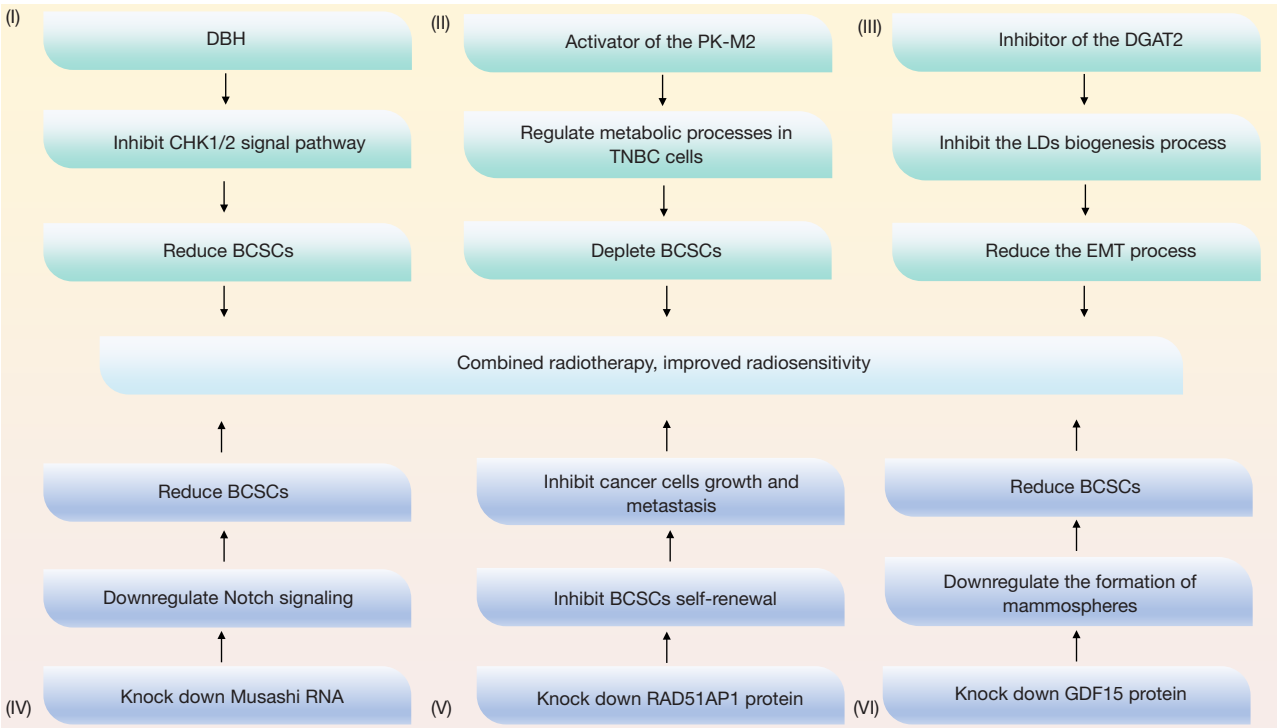

Figure 3 The process of combination therapy to improve radiosensitivity by reducing BCSCs or the EMT process. (I) DBH, an inhibitor of the activated CHK1/2 enzyme, inhibited the CHK1/2 signal pathway. (II) The activator of the PK-M2 enzyme regulated the metabolic processes in TNBC cells. (III) The inhibitors of DGAT2 enzyme inhibited the LDs biogenesis process, and reduced the EMT process. (IV) Knockdown of Musashi RNA can reduce the expression of BCSC markers by downregulating the Notch pathway. (V) Knockdown of the RAD51AP1 protein can reduce the self-renewal of BCSCs, and inhibit the cancer cells growth and metastasis. (VI) Knockdown of the GDF15 protein downregulated the formation of mammospheres. These combined with RT, improved radiosensitivity in breast cancer cells. DBH, debromodiazepine; CHK1/2, checkpoint kinases CHK1 and CHK2; BCSCs, breast cancer stem cells; PK-M2, pyruvate kinase isozyme type M2; TNBC, triple-negative breast cancer; DGAT2, diacylglycerol acyltransferase 2; LDs, lipid droplets; EMT, epithelial-to-mesenchymal transition; RT, radiation therapy.

inhibiting irradiation-induced autophagy. The miR-200c/UBQLN1-mediated autophagy pathway may become a therapeutic target for the treatment of breast cancer. MiR-27a was significantly overexpressed in TNBC (49), and an additional (50) experiment found that miR-27a directly regulated the response of TNBC cells to radiotherapy by downregulating CDC27 protein. It was demonstrated that downregulation of miR-27a resulted in enhanced radiation sensitivity of TNBC cells and that the expression of the CDC27 protein may be a useful marker for assessing the effect of radiotherapy in patients with breast cancer. Zhang and colleagues (51) showed that the expression of miR-22 and sirt1 protein was related to the radiotherapy sensitivity of breast cancer cells and that miR-22 may inhibit the proliferation of tumor cells, promote apoptosis, and improve the radiosensitivity of breast cancer cells by downregulating the expression of sirt1 protein. Therefore, they concluded that miR-22 might be a promising therapeutic target for the treatment of breast cancer. Sun and collaborators found that miRNA Let-7d can suppress the self-renewal ability of CSCs by inhibiting the cyclin D1/Akt1/Wnt1 pathway. Therefore, they indicated that Let-7d may be a promising target for the treatment of TNBC (52). One study (53) found that miR-142-3p overexpression was significantly related to BCSC characteristics. miR-142-3p can decrease the activity of β-linked proteins and the expression levels of some proteins, including CD133, CD44, Bod and ALDH. Furthermore, miR-142-3p can regulate the formation of mammospheres and decrease the radioresistance of breast cancer. They concluded that miR-142-3p may be a potential target for the radiation of BCSCs. A previous study demonstrated that the overexpression of miR-139-

5p was related to DNA repair and ROS genes. DNA repair and ROS genes can induce the apoptosis of breast cancer cells by RT (54). A recent study indicated that the miR-1290/NLRP3 signaling axis was a novel therapeutic target. At the same time, scholars (55) observed that miR-1290 was overexpressed in radioresistant TNBC and that tumor radioresistance was increased by regulating the miR-1290/NLRP3 pathway and mediating the pyroptosis of TNBC (56). In radioresistant breast cancer cells, miR-122 functions as an oncogene and oncogenic miRNA. MiR-122 may promote the radiosensitivity of breast cancer cells by regulating the expression of some transcription factors, including ZNF611 and ZNF304. One study (57) found that miR-16-5p can influence radiotherapy sensitivity and may be a predictive biomarker for the prognosis of breast cancer patients who received radiotherapy.

Wang and colleagues (58) demonstrated that long non-coding RNA (lncRNA) LINC02582, which is the direct target of miR-200c, may enhance the sensitivity of breast cancer cells to RT by downregulating the miR-200c/LINC02582/USP7/CHK1 signaling axis. Their experimental results suggested that the above signaling axis may be a potential target for the clinical therapy of patients with breast cancer. Nonhomologous end joining (NHEJ) is one of the major pathways for repairing damaged DNA in cancer cells. LncRNA LINP1 in the NHEJ pathway was overexpressed in TNBC. Zhang and colleagues (59) found that lncRNA LINP1 can enhance the repair of DNA double-strand breaks (DSBs) by coordinating the NHEJ pathway and that EGFR activation leads to upregulation of LINP1 and that p53 activation downregulates LINP1 expression. They demonstrated that blocking LINP1, which was regulated by the p53 and EGFR signaling pathways, increased the sensitivity of breast cancer tumor cells to radiotherapy. CCAT1 is an important and cancer-causing lncRNA in breast cancer. High expression of CCAT1 was found in radiation-resistant breast cancer cells. Meanwhile, they demonstrated that downregulation of CCAT1 can reduce colony formation of cancer cells, promote apoptosis of cancer cells by upregulating the expression of miR-148b, and improve the radiosensitivity of breast cancer cells (60). Zhang *et al.* (61) found that the knockdown of lncRNA LINC00963 in breast cancer cells inhibited tumor progression and improved radiation sensitivity by regulating the miR-324-3p/ACK1 pathway. miR-139-5p and LINC00963 might be potential targets for breast cancer radiation. A study (62) has been shown that lncRNA HOTAIR was overexpressed in advanced breast cancer cells. The lncRNA HOTAIR can enhance the radioresistance of breast cancer cells by regulating the translation of the *HOXD10* gene and the PI3K/Akt-BAD signaling pathway. Zhang and collaborators (63) demonstrated that lncRNA HOTAIR upregulated the expression of HSPA1A, which belongs to heat shock protein family A, by sequestering miR-449b-5p and improving radiation resistance in breast cancer. It (64) was also found that HOTAIR was overexpressed in invasive ductal carcinoma tissues, and they observed that HOTAIR overexpression promoted the expression of the DNA damage repair factors KU70, KU80, DNA-dependent protein kinase (DNA-PK), and ATM, which could be impeded by small molecular inhibitors of the enhancer of zeste homolog 2 (EZH2). Consequently, HOTAIR may be a marker of breast cancer radiotherapy. In another study, breast cancer cells without HOTAIR expression had high sensitivity to radiotherapy by upregulating the expression level of miR-218. These results suggested that the lncRNA HOTAIR-miR-218 axis may be a new target for radiotherapy sensitization (65). A recent study (66) revealed that lncRNA AFAP1-AS1 can increase the radioresistance of TNBC by activating the Wnt/β-linked protein signaling pathway. In their experiments, they silenced the expression of lncAFAP1-AS1 by constructing a carrier [poly(disulfide amide) (PDSA) NPs] and transporting siAFAP1-AS1 to tumor cells. This lncRNA AFAP1-AS1 could provide useful and prognostic information for TNBC patients who received radiotherapy, and the combined therapy of siAFAP1-AS1 and radiotherapy may be a useful treatment strategy for recurrent TNBC. Alpha-enolase (ENO1) was a major enzyme that modulates glycolysis, which promoted breast cancer cell growth and progression, and proved to be a poor survival marker in breast cancer patients (67). Ma *et al.* (68) found that the ENO1 enzyme enhanced radioresistance by decreasing the intracellular production of ROS and apoptosis in breast cancer cells by modulating mitochondrial homeostasis. Moreover, LINC00663 regulated ENO1 protein stability by enhancing the E6AP-mediated ubiquitin-proteasome pathway. They suggested that inhibition of ENO1 or upregulation of LINC00663 expression could be a potential therapeutic strategy to increase radiosensitivity in breast cancer cells. We summarized the above relevant noncoding RNAs that affect radiosensitivity (*Table 3*). Circular RNAs (circRNAs) belong to ubiquitous endogenous noncoding RNAs, He *et al.* (69) sequenced analysis of TNBC cells after RT, and they found that circNCOR1 upregulated the expression of CDK2 protein by absorbing hsa-miR-638,

Table 3 The effects of different noncoding RNAs on the radiosensitivity of breast cancer cells

Noncoding RNA	Target gene/protein or signaling pathway	Effects	Reference
Upregulation of miRNA-200c	Suppression of the protein expression of the UBQLN1	Inhibition of autophagy and upregulation of radiosensitivity	Sun *et al.* (48)
Upregulation of miRNA-200c	Downregulation of the lncRNA LINC02582	Downregulation of the CHK1 and upregulation of radiosensitivity	Wang *et al.* (58)
Upregulation of miRNA-27a	Suppression of protein expression of the CDC27	Downregulation of radiosensitivity	Ren *et al.* (50)
Upregulation of miRNA-22	Suppression of protein expression of the sirt1	Inhibition of proliferation, promotion of apoptosis and upregulation of radiosensitivity	Zhang *et al.* (51)
miRNA Let-7d	Inhibition of the cyclin D1/Akt1/Wnt1 pathway	Inhibition of self-renewal ability in the CSCs and upregulation of radiosensitivity	Sun *et al.* (52)
Upregulation of miRNA-142-3p	Reduction of the β-linked protein activity	Downregulation of the CSCs and upregulation of radiosensitivity	Troschel *et al.* (53)
Upregulation of miRNA-139-5p	Inhibition of the DNA repair and ROS gene expression	Promotion of apoptosis and upregulation of radiosensitivity	Pajic *et al.* (54)
Upregulation of miRNA-1290	Regulation of the NLRP3 pathway	Inhibition of the pyroptosis and downregulation of radiosensitivity	Li *et al.* (55)
Upregulation of miRNA-122	Regulation of the ZNF611 and ZNF304 transcription factor expression	Upregulation of radiosensitivity	Perez-Añorve *et al.* (56)
Upregulation of lncRNA CCAT1	Downregulation of the miR-148b expression	Upregulation of the colony-forming ability, inhibition of apoptosis and upregulation of radiosensitivity	Lai *et al.* (60)
Downregulation of lncRNA LINC00963	Regulation of the miR-324-3p/ACK1 pathway	Inhibition of tumor activity and upregulation of radiosensitivity	Zhang *et al.* (61)
Upregulation of lncRNA HOTAIR	Regulation of the translation of the *HOXD10* gene and PI3K/Akt-BAD signaling pathway	Downregulation of radiosensitivity	Zhou *et al.* (62)
LncRNA HOTAIR	Sequestration of miR-449b-5p and upregulation of the expression of oncogene HSPA1A	Downregulation of radiosensitivity	Zhang *et al.* (63)
LncRNA HOTAIR	Promotion of DNA repair and regulation of the EZH2	Downregulation of radiosensitivity	Qian *et al.* (64)
Downregulation of lncRNA HOTAIR	Upregulation of the miR-218 expression	Upregulation of radiosensitivity	Hu *et al.* (65)
Downregulation of lncRNA LINP1	Reduction of the DNA repair	Upregulation of radiosensitivity	Zhang *et al.* (59)
Downregulation of lncRNA FAP1-AS1	Inhibition of the Wnt/β-linked protein signaling pathway	Upregulation of radiosensitivity	Bi *et al.* (66)
Upregulation of LINC00663	Downregulation of the ENO1 expression	Upregulation of radiosensitivity	Ma *et al.* (68)

LncRNA, long non-coding RNA; ROS, reactive oxygen species; CHK1, checkpoint kinase 1; CSCs, cancer stem cells; EZH2, enhancer of zeste homolog 2; sirt1, Silent information regulator 1.

thereby promoted cell proliferation and decreased the radiosensitivity of TNBC cells during radiotherapy.

Different signaling pathways affect radiotherapy sensitivity by regulating the expression of related proteins

Kim and colleagues (70) found that radiation can activate the SRC, PI3K and p38 MAPK signaling pathways successively. The activation of signaling pathways can promote the EMT process and increase the radioresistance of breast cancer. Additionally, their study suggested that combination therapy with medicine targeting SRC and RT may attenuate the malignant phenotype induced by radiation and provide a good therapeutic effect for breast cancer. An experimental study (71) observed that the activation of extracellular signal-regulated kinase (ERK) signaling was associated with tumor stemness and EMT phenotype, which was an important method for acquiring radioresistance in breast cancer cells. Recently, it (72) has shown that the activation of the ribosomal S6 kinase (RSK) and Akt signaling pathways can inhibit the DNA DSB repair process induced by radiation and improve the radiosensitivity of breast cancer cells. SIRT1 is an enzyme that can deacetylate histone and nonhistone proteins. IL-6 is involved in tumor progression as a cytokine, and the function of IL-6 is dependent on the activity of SIRT1 (73). The PI3K/Akt/mTOR pathway was regulated by SIRT1 and IL-6. inhibitors of PI3K and mTOR and SIRT1 activators can effectively induce the apoptosis of breast cancer cells and enhance the radiotherapy sensitivity of breast cancer cells (74,75). Phosphorylated ribosomal S6 kinase 1 (p-S6K1) is a key effector of the mTOR pathway. Choi *et al.* (76) found that high expression of p-S6K1 was associated with radioresistance in breast cancer patients. They concluded that the p-S6K1 protein might serve as an important marker for predicting radiotherapy resistance and that the p-S6K1 protein can function as a new target for radiosensitization. A study found that carnitine palmitoyltransferase I (CPT1) and carnitine palmitoyltransferase II (CPT2) were rate-limiting enzymes for mitochondrial fatty acid transport in radiation-resistant breast cancer cells. Enhanced expression levels of CPT1/CPT2 were associated with poor prognosis in breast cancer patients. The study demonstrated that the inhibition of CPT1/CPT2 can block the fatty acid oxidation process, downregulate the ERK pathway, inhibit invasiveness, and enhance the sensitivity of breast cancer cells to RT (77). Another study (78) found that the inhibition of signal transducer and activator of transcription 3 (STAT3) and survivin, which is a STAT3 target gene, can enhance the radiosensitivity of HER2-positive breast cancer cells. They suggested that the STAT3-survivin signaling pathway may serve as a predictive marker of radiotherapy sensitivity. CD47 is a myeloid-specific immune checkpoint protein. A study has also been shown that dual blockade of HER2 and CD47 plays an important role in eliminating the radioresistance of HER2-positive breast cancers (79). Some results showed that high expression of estrogen receptor 1 (ESR1) was significantly associated with poor overall survival of breast cancer patients. ESR1 can enhance the binding of the E3 ubiquitin ligase NEDD4L and CD71 protein and promote the ubiquitination and degradation of the CD71 protein. They demonstrated that ESR1 knockdown significantly enhanced iron death induced by RT and increased the expression of the CD71 protein. The results showed that the ESR1/NEDD4L/CD71 axis might be a potential target for breast cancer radioresistance (80). One experiment (81) reported high levels of expression of Notch ligand Dll1 and activated cancer-associated fibroblasts (CAFs) in irradiated tumor samples from luminal breast cancer patients. They found that Dll1-mediated Notch signaling, which increased Wnt ligand secretion, increased the number of BCSCs and CAFs, which promoted metastasis and radioresistance. A study (82) found that inhibition of the VEGF/neuropilin-2 (NRP2) pathway reduced the expression of antioxidant genes by reducing the level of nitric oxide synthase 2 (NOS2)/nitric oxide (NO), consequently, improved the radiosensitivity of TNBC. The effects of the above different signaling pathways on the sensitivity of radiotherapy were also summarized (*Table 4*).

Radiotherapy sensitivity-related genes

We have summarized the following genes that affect sensitivity to radiotherapy (*Table 5*). Huang *et al.* (83) found that the expression of the *TPX2* gene was closely associated with BCSCs in tumor tissues and played an important role in the prediction of radioresistance and prognosis for breast cancer patients. He and colleagues (84) found that HER2-positive and BRCA1-negative breast cancer patients had radiotherapy resistance and poor prognosis. Sun *et al.* (85) found that overexpression of the *ALG3* gene was related to the radioresistance of breast cancer. Regulating the glycosylation of TGF-β receptor II and activating the TGF-β signaling pathway can promote the radioresistance of breast cancer cells. They suggested that *ALG3* may serve

Table 4 The effects of different signaling pathways on the radiosensitivity of breast cancer

Signaling pathways	Mechanisms	Effects	References
SRC-PI3K/p38-MAPK pathway	Promotion of the EMT process in breast cancer cells	Upregulation of radiosensitivity	Kim *et al.* (70)
ERK pathway	Reduction of the cancer stemness and the EMT phenotype in breast cancer cells	Upregulation of radiosensitivity	Paramanantham *et al.* (71)
PI3K/Akt/mTOR pathway	Induction of the apoptosis in breast cancer cells	Upregulation of radiosensitivity	Masoumi *et al.* (74); Gasimli *et al.* (75)
mTOR/p-S6K1 pathway	high expression of p-S6K1 was associated with radioresistance	p-S6K1 expression status as an important marker for predicting the radioresistance	Choi *et al.* (76)
HER2-STAT3-survivin pathway	Induction of the death in breast cancer cells	Upregulation of radiosensitivity	Kim *et al.* (78)
ESR1/NEDD4L/CD71 pathway	Enhancement of the RT-induced iron death in breast cancer cells	Upregulation of radiosensitivity	Liu *et al.* (80)
Dll1/Notch pathway; VEGF/NRP2 pathway	Upregulation of BCSCs and CAFs; reduction of the antioxidant gene expression	Downregulation of radiosensitivity; upregulation of radiosensitivity	Nandi *et al.* (81); Kumar *et al.* (82)

EMT, epithelial-to-mesenchymal transition; p-S6K1, phosphorylated ribosomal S6 kinase 1; RT, radiation therapy; BCSCs, breast cancer stem cells; CAFs, cancer-associated fibroblasts.

Table 5 The effects of different genes on radiosensitivity of breast cancer

Genes	Regulation of radiosensitivity to breast cancer	References
TPX2	The *TPX2* gene expression may play an important role in predicting radioresistance and prognosis in breast cancer stem cells	Huang *et al.* (83)
HER2 and *BRCA1*	High expression of *HER2* and low expression of *BRCA1* may associated with radioresistance in breast cancer patients	He *et al.* (84)
ALG3	Overexpression of *ALG3* gene, activation of TGF-β signaling pathway, and upregulation of radioresistance in breast cancer patients	Sun *et al.* (85)
FATS	The *FATS* status as a biomarker of radioresistance in breast cancer patients	Zhang *et al.* (86)
ZNF gene family	High expression of ZNF644 and upregulation of radiosensitivity; low expression of ZNF341/ZNF544/ZNF653 and downregulation of radiosensitivity in breast cancer patients	Yan *et al.* (87)
DAB2IP	The *DAB2IP* gene expression was downregulated in breast cancer cells, leading to radioresistance.	Zhang *et al.* (88)

TPX2, Xenopus kinesin-like protein 2; *FATS*, fragile-site associated tumor suppressor; *ZNF*, zinc finger protein; ALG, asparagine-linked glycosylation; TGF-β, transforming growth factor beta.

as a potential radiosensitivity marker.

In a study, Zhang and colleagues (86) demonstrated that the fragile-site associated tumor suppressor (FATS) was positively related to the prognosis of breast cancer patients who were treated with RT. They also found that the quantitative detection of FATS mRNA levels in tissues from breast cancer patients can predict radioresistance. Yan and collaborators (87) explored the relationship between the expression of the zinc finger protein (*ZNF*) gene and the radiosensitivity of breast cancer using the public The Cancer Genome Atlas (TCGA) and METABRIC databases. They found that breast cancer patients with high expression of ZNF644 protein were sensitive to RT. The results also showed that the low expression of *ZNF* family genes,

including ZNF653, ZNF544, and ZNF314 proteins, was related to radioresistance. Zhang and colleagues (88) found that the expression of the *DAB2IP* gene was downregulated in breast cancer cells, and their data supported that loss of *DAB2IP* led to increased hypoxia, inhibited vascular maturation and promoted the formation of vasculogenic mimicry (VM), leading to radioresistance in breast cancer cells. Yin *et al.* (89) performed genome-wide clustered regularly interspaced short palindromic repeats (CRISPR)/Cas9 screening to determine the response of breast cancer cells to RT. They identified BCL2 family proteins, and treatment with inhibitors targeting these proteins led to radiosensitization both *in vitro* and *in vivo*, possibly by enhancing apoptosis after radiotherapy.

Other methods or drugs that affect sensitivity to RT

Güttler (90) and his team found that the inhibition of carbonic anhydrase IX activity affected the pH value of intracellular extracellular and clonal survival and induced apoptosis of breast cancer cells that were treated with RT. It (91) has been shown that HSP90 inhibitors can enhance the sensitivity of tumor cells to radiation. Some experiments (92) investigated the effect of the HSP90 inhibitor PU-H71 on metastatic breast cancer cells alone or in combination with RT, and they found that PU-H71 can enhance the therapeutic effect of RT, especially in metastatic breast cancer cells. It (93) was also found that the combination of octreotide acetate and RT can enhance radiosensitivity and induce the apoptosis of MCF7 cells. The above findings showed that octreotide acetate has a potential role as a radiosensitizing agent. Ultrasound-sensitive oxygen microbubbles (OMBs), which locally release oxygen into tumor tissue, were an innovative approach to the problem of tumor hypoxia (94). Some scholars (95) found that both two-week metformin therapy and OMBs treatment normalized the abnormal cancer vascular system. The combination of metformin and OMB produced more dramatic and sustained results than either treatment alone. They found the combination treatment led to an increased radiosensitivity in breast cancer cells. In addition, exosomes are extracellular vesicles secreted by most tumor cells, and some experimental studies have demonstrated that exosomes can serve as an effective tool for promoting a radioresistant phenotype in breast cancer cells. They suggested that exosomes are potential therapeutic targets of radioresistance (96). POU class 3 homeobox 2 (POU3F2) is a member of the POU3 family of transcription factors. Zhang (97) and colleagues found that the *POU3F2* gene was upregulated in TNBC cells, and *POU3F2* enhanced the activation of the Akt pathway, which promoted proliferation and radioresistance in TNBC cells. They suggested that targeting *POU3F2* may be a potential strategy to overcome radioresistance. Park *et al.* (98) found that the PARP inhibitor, olaparib, combined with radiation specifically increased DNA damage and apoptosis in breast cancer cells, and combining olaparib with an ATR inhibitor further enhanced the radiosensitizing effect of protons. Natural anmindenol A was isolated from the marine-derived bacterium *Streptomyces* spp. AM-18002 was a derivative of anmindenol A. Eum *et al.* (99) found that the combination of AM-18002 and radiation acted as a potent anticancer agent by increasing ROS production and blocking myeloid-derived suppressor cells-mediated STAT3 activation in breast cancer cells. Polo-like kinase 4 (PLK4) is a regulator of centriole duplication, and Pellizzari *et al.* (100) found that inhibition of PLK4 significantly enhanced the anticancer effects of RT in TNBC, and their findings supported further mechanistic studies of anti-PLK4 agents and radiotherapy as a novel multimodality combination treatment strategy in TNBC.

Potential markers for radiotherapy sensitivity prediction

Drobin and colleagues (101) analyzed some blood samples of breast cancer patients who were sensitive to RT and found that some proteins, including CHIT1, PDGFB, PNKD, RP2, SERPINC1, SLC4A, STIM1, and THPO, can predict the sensitivity of breast cancer patients to RT. A study (102) illustrated that the pretreatment neutrophil-lymphocyte ratio (NLR) was correlated with the prognosis of breast cancer patients. A working group (103) recruited 130 patients with stage II–III TNBC and found that an elevated NLR in serum samples after RT was an independent prognostic biomarker for the local recurrence rate, progression-free survival and overall survival time of patients with stage II–III TNBC. Some scholars (104) found that DKK1 and GNPNAT proteins were radiation-induced secreted proteins and that DKK1 and GNPNAT proteins can function as predictive biomarkers of radiosensitivity. They suggested that these biomarkers could provide personalized information on clinical treatment, including RT dosing and RT regimens.

In a retrospective study (105), the expression of

synaptic nuclear protein-γ (SNCG) was assessed by immunohistochemistry in breast cancer patients who received RT after mastectomy. The results showed that the positive expression of SNCG could be related to radioresistance in breast cancer patients. A clinical trial (106) identified that the low expression of stromal platelet-derived growth factor receptor-β can function as a marker of radiosensitivity for breast cancer patients with ductal carcinoma *in situ*. It has been shown that the fidelity of DNA repair can be used as a marker for predicting the prognosis of breast cancer patients who receive radiotherapy (107). Abdollahi *et al.* (108) collected blood from 60 patients with invasive ductal breast cancer and 20 healthy women and used a standard G2 chromosome assay categorized as two equal groups of patients with and without cellular radiosensitivity. Real-time quantitative PCR detecting system was used to detect the expression levels of circ-FOXO3 and miR-23a in peripheral blood mononuclear cells. circ-FOXO3 was found to be downregulated and miR-23a was up-regulated in patients with breast cancer, and they suggested that circ-FOXO3 and miR-23a may be potential biomarkers for predicting the sensitivity of breast cancer to radiosensitization.

Conclusions

In this paper, we reviewed the literature and summarized the latest research advances on the radiosensitivity of breast cancer patients. This review paper includes the following six aspects: the immune microenvironment, tumor stem cells, signaling pathways, regulation of gene/protein expression, small molecule drugs, and predictive markers for radiosensitivity.

Radiotherapy is an important method for the comprehensive treatment of breast cancer. The predictive factors of breast cancer radiosensitivity can help oncologists predict the efficacy of RT, formulate individualized radiotherapy regimens and adjust comprehensive treatment plans for breast cancer patients. There are still some deficiencies in this review article. Most of the studies that were included in this review article have been based only on cell or animal experiments, and only a few experiments have been validated by clinical samples. Our future studies should pay more attention to the clinical and translational research of radiosensitization targets.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-24-71/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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