



# Targeting Epithelial-to-Mesenchymal Transition in Radioresistance: Crosslinked Mechanisms and Strategies

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Radiotherapy exerts a crucial role in curing cancer, however, its treatment efficiency is mostly limited due to the presence of radioresistance. Epithelial-to-mesenchymal transition (EMT) is a biological process that endows the cancer cells with invasive and metastatic properties, as well as radioresistance. Many potential mechanisms of EMT-related radioresistance being reported have broaden our cognition, and hint us the importance of an overall understanding of the relationship between EMT and radioresistance. This review focuses on the recent progresses involved in EMT-related mechanisms in regulating radioresistance, irradiation-mediated EMT program, and the intervention strategies to increase tumor radiosensitivity, in order to improve radiotherapy efficiency and clinical outcomes of cancer patients.

**Keywords:** EMT, radioresistance, mechanisms, strategies, cancer stem cell, tumor microenvironment

## 1 INTRODUCTION

Radiotherapy has always been an effective therapy for cancers. More than half of cancer patients are treated with radiotherapy alone or in combination with other treatments. It primarily exerts its role by direct physical damage to DNA or indirect damage from reactive oxygen species. Despite the appreciable advances in radiotherapy in recent years, most cancer patients remain poor prognosis. Tumor radioresistance has been considered as a powerful obstacle to impinge on radiotherapy efficacy, and EMT acts as one of the most important factors involving radioresistance (1, 2). Epithelial-to-mesenchymal transition (EMT) is a biological process that refers to the transition of epithelial cells to ones with mesenchymal phenotype. This process is generally accompanied by the alterations in cell morphology, cell-cell adhesion and cellular signaling factors. It is characterized by the loss of epithelial adhesion markers (E-cadherin) and the gain of mesenchymal markers such as N-cadherin, vimentin, fibronectin and alpha smooth muscle actin (α-SMA) (3).

In this review, we conduct a comprehensive review focusing on the recent advances in EMT-related mechanisms in regulating radioresistance and the influence of irradiation on EMT, and excavate the potential strategies to overcome radioresistance.

## 2 EMT-MEDIATED MECHANISMS IN RADIORESISTANCE

EMT is known to play a central role in inducing resistance of tumor cells to irradiation, and it is regulated by a variety of molecular mechanisms containing TGF- $\beta$ , Wnt/ $\beta$ -catenin, PI3K/AKT, Notch, NF- $\kappa$ B, IL-6/STAT3, non-coding RNAs and so on. Also, cancer stem cells and tumor microenvironment participate in the acquisition of EMT program and tumor radioresistance. These mechanisms function mainly depending on the activation of EMT-related transcription factors (TFs) and markers, including Snail/Slug, ZEB1/2, Twist1/2, E-cadherin, N-cadherin, Vimentin (4–7). EMT-related mechanisms in regulating radioresistance are depicted in **Table 1**.

### 2.1 Signaling Pathways in Radioresistance

#### 2.1.1 TGF- $\beta$ Pathway

The TGF- $\beta$  family works as an important inducer in EMT program. For instance, the TGF- $\beta$ , Activin and Nodal, can induce EMT in

epithelial cells under different circumstances (64). It was once thought that TGF- $\beta$  mainly exerted suppressive roles in tumorigenesis due to its ability to inhibit epithelial cell growth and induce cell apoptosis. However, subsequent studies discovered that high levels of TGF- $\beta$  promoted tumor infiltration and metastasis by inducing EMT. TGF- $\beta$  acts on target cells through binding to specific receptors, resulting in downstream phosphorylation of Smad2 and Smad3. Phosphorylated Smads form a transcriptional complex with the cofactor Smad4, which enters into the nucleus and binds to specific gene promoters to regulate gene transcription (65). It has been reported that overexpression of Smad2/3 promotes TGF- $\beta$ -induced EMT, whereas its dominant negative form can abolish the EMT phenotype (66). Besides, the non-Smad-dependent TGF- $\beta$  pathway is also shown to be associated with EMT process, in which p38 is one of commonly studied molecules. In mouse mammary epithelial NMuMG cells, TGF- $\beta$  could phosphorylate and activate p38 protein, which is required for EMT process. Synergistic stimulation of TGF- $\beta$  and TNF- $\alpha$  to induce the morphological alteration from dense epithelial cells to dispersed mesenchymal cells in human colon cancer models is also dependent on enhanced p38 activity (67). In addition, classical protein kinases such as PKA and PKD also play a key role in TGF- $\beta$ -induced EMT (68, 69). Inhibition of TGF- $\beta$  pathway strongly blocked the EMT and cancer stem cell (CSC) program, conferring an increase of radiosensitivity (8). In breast cancers, Konge J et al. established the

**TABLE 1** | EMT-mediated mechanisms in radioresistance.

Mechanism	Targeted molecule	Function	Radiotherapy effect	Reference
Signaling pathways	TGF- $\beta$	EMT-mediated CSC program; regulate expression of EMT markers	Radioresistance	(8–10)
	Wnt/ $\beta$ -catenin	Modulate EMT-related genes expression; increase ALDH activity	Radioresistance	(11–14)
	PI3K/AKT	Regulate expression of Snail, Twist and EMT markers	Radioresistance	(15–18)
	Notch	Promote the expression of ZEB1, Slug, Snail, NF- $\kappa$ B and Vimentin	Radioresistance	(19–21)
	NF- $\kappa$ B	Regulate Twist, Snail and SIP1	Radioresistance	(22–25)
	IL-6/STAT3	Regulate the expression of Zeb1 and mesenchymal markers	Radioresistance	(26, 27)
	S1PR1	Activate STAT3 and promote CSC program	Radioresistance	(28–30)
Non-coding RNAs	miR-124	Targeting an EMT inducer PRRX1	Radiosensitivity	(31)
	miR-145	Regulate ZEB2 expression	Radiosensitivity	(32)
	miR-205	Regulate PTEN/PI3K/AKT signaling	Radioresistance	(33)
	miR-624-3p	Modulate PTEN/PI3K/AKT signaling	Radiosensitivity	(34)
	miR-301a	Wnt1-dependent EMT	Radiosensitivity	(35)
	LncRNA-TUG1	Target the miR-145/ZEB2 axis	Radioresistance	(32)
	LncRNA-NEAT1	Target the miR-204/ZEB1 axis	Radioresistance	(36)
Cancer stem cells	LncRNA-UCA1	Regulate the expression of MMP-9, ZEB1 and Vimentin	Radioresistance	(37)
	EMT-TF	EMT-TF-induced EMT program provokes the acquisition of tumor-initiating CSCs by regulate stem-cell markers	Radioresistance	(38)
	CD29	Induce EMT phenotype, and facilitate the radioresistance via modulating	Radioresistance	(39)
	CD44	ILK-AKT-mTORC1 signaling	Radioresistance	(40, 41)
Tumor microenvironment	TAMs	Drive EMT process via PI3K/AKT, Wnt/ $\beta$ -catenin or ERK pathways	Radioresistance	(42–50)
	T cells	Regulate PI3K/AKT, HIF-1 $\alpha$ , EGFR/ERK1/2, TGF- $\beta$ , JAK/STAT signaling pathways	Radioresistance	(51, 52)
	Neutrophils	Facilitate the expression of FN1, VIM, TGM2 and ZEB1; increase the secretion of IL-6	Radioresistance	(53)
	NK cells	Exacerbate hypoxia microenvironment and stabilize Snail	Radioresistance	(54)
	Mast cells	Increase stemness and expression of EMT markers and morphologic switching	Radioresistance	(55)
	Exosomes derived from T cells	Release IL-8 to induce EMT	Radioresistance	(56)
	CAFs	Increase the $\beta$ -catenin expression and activate the NF- $\kappa$ B/snail pathway	Radioresistance	(57–60)
	CAFs	Induce paracrine TGF- $\beta$ ; reduce a lot of cytokines and growth factors, such as IL-6, EGF, VEGF and HGF	Radioresistance	(57–60)
	Hypoxia	Activate TGF- $\beta$ , NF- $\kappa$ B and Notch pathways; promote the expression of Zeb1, Snail and Twist; regulate the expression of EMT markers	Radioresistance	(61–63)

cell model with EMT phenotype induced by TGF- $\beta$ , they found that these cells acquired the CSC properties, and exhibited enhanced radioresistance (9). Besides, in nasopharyngeal carcinoma (NPC), TGF- $\beta$  could promote tumor invasion and EMT process by decrease of E-cadherin and increase of Vimentin, thus enhancing the resistance of cancer cells to irradiation (10).

### 2.1.2 Wnt/ $\beta$ -Catenin Pathway

Activation of Wnt/ $\beta$ -catenin signaling is important in regulating stemness, metastasis, and proliferation of malignant tumors, and recent studies have also shown that it is implicated in tumor radioresistance by inducing EMT (70, 71). Bastos LG et al. (11) reported that Wnt/ $\beta$ -catenin signaling could promote the radioresistance and metastasis of NPC cells by increasing nuclear translocation of  $\beta$ -catenin and transcriptional upregulation of EMT-related genes expression. Another study reported that Wnt/ $\beta$ -catenin pathway triggered the acquisition of EMT phenotype by modulating the activity of aldehyde dehydrogenase (ALDH), thus improving the resistance of prostate cancer progenitor cells to irradiation (12). Inhibition of the Wnt/ $\beta$ -catenin pathway using a  $\beta$ -Catenin/TCF inhibitor FH535, could reverse EMT phenotype and enhance the radiosensitivity of esophageal cancer cells (13). Besides, knockdown of FOXO3a contributed to the transition of EMT phenotype by activating Wnt/ $\beta$ -catenin pathway, thereby resulting in radioresistance (14).

### 2.1.3 PI3K/AKT Pathway

PI3K/AKT pathway is frequently activated in various human cancers, and has been considered a promising therapeutic target. Increasing studies demonstrated that PI3K/AKT pathway played a crucial role in cell proliferation, survival, metastasis and EMT (72, 73). PI3K/Akt pathway participates in the regulation of Snail, one of the most important EMT-TFs by multiple mechanisms. First, PI3K/Akt activation can promote the phosphorylation of GSK-3 $\beta$ , which accelerates the ubiquitination and degradation of GSK-3 $\beta$ , thus decreasing its degradation to Snail (15). Second, Snail can be directly regulated by PI3K/Akt pathway (16). Twist, another EMT-associated TF, is also positively regulated by PI3K/Akt signaling (16). Several studies have reported that activation of PI3K/Akt pathway is instrumental in enhancement of radioresistance of cancer cells by modulating the expression of EMT markers (17, 18). Besides, in non-small cell lung cancer (NSCLC) cells, PI3K/AKT pathway activated by miR-410/PTEN, functions as an important promotor in occurrence of EMT and radioresistance (74).

### 2.1.4 Notch Pathway

Notch signaling exerts a crucial role in carcinogenesis by regulating tumor microenvironment or EMT (75, 76). Activation of Notch signaling is triggered by ligand-binding to generate intracellular domain of Notch1 (ICN1), which forms a transcriptional complex with the transcriptional factor CSL/RBPJ and other co-activators such as mastermind-like 1 (MAML1) and EP300, thus promoting the transcription of target genes such as the family of HES/HEY (77). Notch pathway activation contributed to the acquisition of EMT. Conversely, down-regulation of Notch signaling by siRNA could partially reverse the EMT phenotype by decreasing the

expression ZEB1, Slug, Snail, NF- $\kappa$ B and Vimentin (19). Furthermore, suppression of Notch signaling by  $\gamma$ -secretase inhibitors or siRNAs could boost the sensitivity of tumor cells to irradiation (20, 21).

### 2.1.5 NF- $\kappa$ B Pathway

Accumulating evidence confirmed the important roles of NF- $\kappa$ B pathway in EMT-mediated radioresistance (2, 78). It has been shown that NF- $\kappa$ B pathway is involved in the regulation of EMT genes such as Twist, Slug and SIP1 in multiple cancers (22, 23). NF- $\kappa$ B activity can be induced by Notch signaling in tumor cells during injuries (79). Blockage of NF- $\kappa$ B activity by Notch inhibition could increase the sensitivity of NSCLC cells to radiotherapy (24). Similarly, inhibition of NF- $\kappa$ B signaling using its dominant-negative regulator A20, also significantly counteracted the formation of EMT and decreased the radioresistance of hepatocellular carcinoma (HCC) cells (25).

### 2.1.6 IL-6/STAT3 Pathway

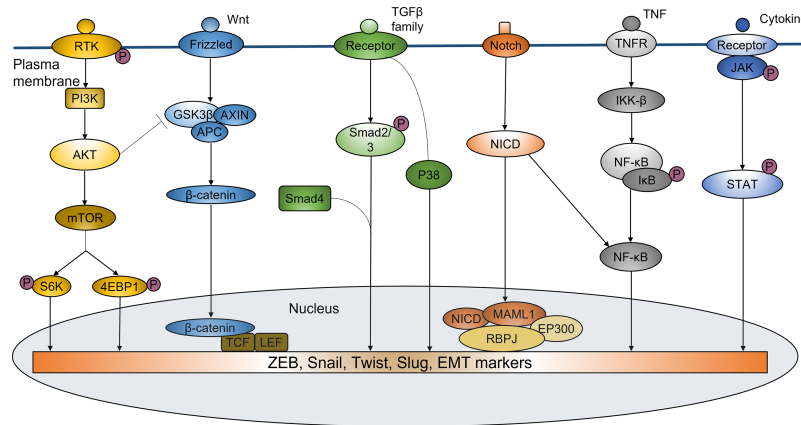
Activation of IL-6/STAT3 signaling has been shown to be instrumental in inducing EMT, which mediates progression and resistance to radiotherapy in many types of malignant cancers. Silence of STAT3 by siRNA blocked STAT3 activation and inhibited the mesenchymal phenotype of pancreatic cancer cells (80). Activation of STAT3 was involved in the regulation of PIM serine/threonine kinase (PIM2) expression, and targeting PIM2, STAT3 or PIM2-dependent cytokines could inhibit invasive and migratory properties of cancer cells possibly through suppression of Zeb1 (26). Blocking IL-6/STAT3 signaling by anti-IL-6 antibodies or STAT3 inhibitor (NSC74859) disturbed stellate cell-induced migration and expression of mesenchymal markers in pancreatic cancer cells (27). In addition, STAT3 knockdown could effectively suppress cancer stem cell-like properties, synergistically enhance the effects of radiotherapy, and significantly improve the survival of immunocompromised mice (81). These findings provide a valuable strategy to inhibit EMT and malignant phenotypes by blocking IL-6/STAT3 signaling.

### 2.1.7 Other Relevant Molecular Mechanisms

Recent studies have identified sphingosine-1-phosphate receptor 1 (S1PR1) as a pro-oncogene that is highly expressed in a variety of malignancies. It plays a crucial role in promoting tumor metastasis and EMT process. The S1PR1 antagonist FTY720 can significantly inhibit EMT program by inactivating STAT3 signaling (82, 83), further modulating the resistance of cancer cells to therapy. Several studies have shown that S1PR1-mediated sustaining activation of STAT3 is of critical importance in proliferation and multidirectional differentiation of CSCs, which is closely associated with acquired radioresistance in a variety of malignancies such as pancreatic cancer and glioma (28–30). EMT-related signaling pathways in mediating radioresistance were shown in **Figure 1**.

## 2.2 Non-Coding RNAs in Radioresistance

Non-coding RNAs including microRNAs (miRNAs) and long non-coding RNAs (lncRNAs) have been considered as the important factors in EMT development and radioresistance by multiple regulatory mechanisms.



**FIGURE 1** | EMT-related signaling pathways in mediating radioresistance. EMT regulated by a variety of signaling pathways plays an important role in inducing radioresistance of tumor cells. PI3K/Akt pathway participates in the regulation of Snail and Twist. PI3K/Akt activation can also increase phosphorylation, ubiquitination and degradation of GSK-3 $\beta$ , thus decreasing its degradation to Snail. Wnt/ $\beta$ -catenin signaling can promote the radioresistance by increasing nuclear translocation of  $\beta$ -catenin and transcriptional upregulation of EMT-related genes expression. TGF- $\beta$  signaling can regulate the expression of EMT markers to induce EMT by Smad or non-Smad-dependent ways, thus enhancing the resistance of cancer cells to irradiation. Notch signaling can increase the expression of ZEB1, Slug, Snail, NF- $\kappa$ B and Vimentin to promote the EMT phenotype. NF- $\kappa$ B pathway has the important roles in EMT-mediated radioresistance. It is involved in the regulation of EMT genes such as Twist, Slug and SIP1. IL-6/JAK/STAT6 pathway can induce EMT by mediating ZEB1 and EMT-related markers, resulting in enhanced tumor resistance to radiotherapy.

### 2.2.1 MiRNAs

MiRNAs belong to small non-coding RNAs and act by inhibiting gene expression post-transcriptionally. One study demonstrated that ectopic miR-613 expression inhibited the proliferation and invasion, and impeded EMT phenotype by increasing expression of epithelial markers and decreasing expression of mesenchymal markers (84). Another study reported that miR30a decreased the invasion and migration of colorectal cancer cells, and its overexpression not only downregulated the expression levels of transmembrane-4-l-six-family-1 (TM4SF1), but inhibited VEGF expression and enhanced E-cadherin expression (85). MiR-3622a could inhibit the EMT by perturbing the expression of EMT effectors Zeb1 and Snail2 (86). All these findings suggest that multiple types of miRNAs exert tumor suppressive effects by counteracting EMT in cancer cells, and it may be a valuable tool for cancer therapy. In human colorectal cancer, miR-124 could sensitize cancer cells to ionizing radiation by directly targeting a new EMT inducer PRRX1 (31). MiR-145 negatively modulated EMT and radioresistance *via* regulating ZEB2 expression in human bladder cancer cells (32). Additionally, miR-205 has been verified to be an enhancer in radioresistance by promoting EMT in esophageal cell squamous carcinoma (ESCC) cells, which is enacted mechanistically through PTEN/PI3K/AKT signaling (33). Likewise, miR-624-3p interacting with CircVRK1 also modulated the radioresistance by this signaling-mediated EMT (34). In ESCC cells, miR-301a is also validated for boosting radiosensitivity by suppressing Wnt1-dependent EMT (35).

### 2.2.2 lncRNAs

Previous study has revealed that upregulation of lncRNA taurine gene 1 (TUG1) could elicit radioresistance by promoting EMT

and targeting the miR-145/ZEB2 axis (32). Similarly, Lu et al. (36) reported that lncRNA-NEAT1 knockdown reversed the EMT phenotype by targeting miR-204/ZEB1 in NPC cells, suggesting that NEAT1 acts as an EMT inducer leading to radioresistance. Yang et al. (37) demonstrated that downregulation of lncRNA-UCA1 decreased the expression of EMT markers, such as MMP-9, ZEB1 and Vimentin, thereby improving radiosensitivity of colorectal cancer cells. As mentioned above, lncRNAs participate in the regulation of radiosensitivity of cancer cells by inducing or inhibiting EMT *via* different mechanisms.

### 2.3 Cancer Stem Cells

CSCs have the capacity of spheroid formation and self-renewal (87), which are randomly distributed in tumors (88), but are mainly localized in hypoxic, low pH and less nutritious ecological niches (89). CSCs play an important role in tumorigenesis, recurrence and metastasis (90–92). They share many features with regenerative stem cells, such as self-renewal and pluripotency (93), as well as their reversible quiescent state (94). However, there are numerous features specific to CSCs, including strong tumorigenic potential, proliferation, ALDH activity, and aberrant cell cycle (95). CSCs have been identified as a rare cell subpopulation within tumors (96, 97), representing 1% of the cells in most solid tumors (98).

EMT is interacted with CSCs in regulating tumorigenesis and development in a variety of cancers. On one hand, EMT works as an important manipulator in the acquisition of stem cell properties (38, 99–105). EMT-TF-induced EMT program provoked the gain of tumor-initiating CSCs by regulating the expression of stem-cell markers in human breast cancer cells (38).



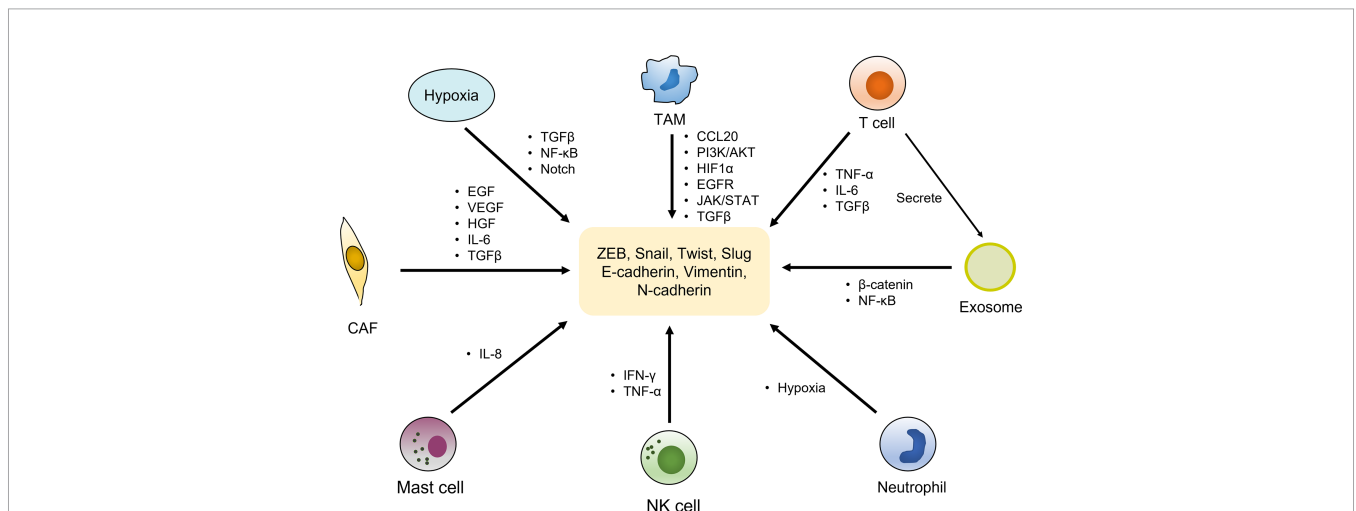
CSCs is also verified to be closely linked with radioresistance (87, 106). In human lung cancer (LC) and NPC cells, the EGFR/PKM2 signaling enhanced the resistance of tumor cells to irradiation by inducing CSC-like features (107). Moreover, the radioresistant NSCLC cells not only showed the EMT phenotype but the enrichment of stemness markers including CD44 and CD133 (108). Therefore, EMT can drive radioresistance through promoting the transition of non-CSCs to CSCs. On the other hand, EMT is considered as a vital process in CSC plasticity (109). Evidence from the study of HCC cells proposed that CD29, one of the most studied CSC markers, was an inducer of EMT phenotype, and facilitated the radioresistance *via* modulating ILK-AKT-mTORC1 signaling (39). Another stemness factor CD44 is also involved in the regulation of radioresistance by driving EMT process *via* PI3K/AKT, Wnt/ $\beta$ -catenin or ERK pathways in prostate and pancreatic cancers (40, 41). These findings shed light on the interaction of EMT with CSCs in mediating radioresistance.

## 2.4 Tumor Microenvironment

Tumor microenvironment (TME) has been confirmed to play a central role in EMT-induced radioresistance. It is composed of cellular and non-cellular components. The former mainly includes lymphocytes, macrophages, cancer-associated fibroblasts (CAFs), vascular endothelial cells and other types of cells, while the latter contains extracellular matrix (ECM), pH, oxygen partial pressure, and various metabolites. There is a complicated crosstalk between cancer cells and TME, interplaying with each other to facilitate tumor initiation and progression. Importantly, the alterations of TME factors strongly impinge on the development of EMT process (110). The roles of TEM in inducing EMT were displayed in **Figure 2**.

After radiotherapy, the number of local immunosuppressive cells such as tumor-associated macrophages (TAMs), myeloid-

derived suppressor cells (MDSCs) and regulatory T cells in tumor tissue is relatively increased owing to their lower radiosensitivity compared to other lymphocyte subtypes (111–113). TAMs are a major component of tumor-infiltrating immunocytes and largely contribute to the immunosuppressive tumor microenvironment. M1-type macrophages efficiently phagocytose tumor cells and release pro-inflammatory cytokines that activate T cells and NK cells, whereas M2-type macrophages have immunosuppressive and TME remodeling functions. Studies showed that TAMs exert a crucial role in inducing EMT. Liu et al. (42) found that in pancreatic cancer, CCL20 released by M2-TAMs could facilitate invasion, metastasis and EMT of cancer cells mainly *via* regulating PI3K/AKT-ERK1/2 signaling pathway. COX-2(+) TAMs promoted the expression of MMP-9 and EMT phenotype in breast cancer cells by activating AKT signaling, thus promoting tumor cell invasion and metastasis (43). Also, M2 macrophages could release an array of cytokines to facilitate EMT *via* regulating multiple signaling pathways (44) such as HIF-1 $\alpha$  (45), EGFR/ERK1/2 (46), Smad/Snail (47) and TGF- $\beta$  (48, 49). Furthermore, TAMs could mediate EMT to promote the migration and invasion of cancer cells, which is associated with activation of JAK2/STAT3/miR-506-3p/FoxQ1 axis (50). Studies have reported that radiotherapy is involved in the regulation of many immune processes, such as antigen release and presentation, T lymphocyte initiation and activation, T cell recruitment and aggregation in tumors, and T lymphocyte recognition and killing of tumor cells (114). In addition to the roles against tumor cells, T cells can also mediate tumor progression. In inflammatory breast cancer (IBC), activated T cells could release soluble factors (TNF- $\alpha$ , IL-6, and TGF- $\beta$ ) to facilitate the expression of EMT-related genes, including FN1, VIM, TGM2 and ZEB1, thereby promoting EMT (51). Moreover, CD4(+) T cells in peritumor secrete large amount of IL-6 in clear cell renal carcinomas (ccRCC), which favors the alteration of tumor cell morphology as well as the acquisition of EMT and stemness



**FIGURE 2** | EMT activation by components of the tumor microenvironment. The tumor microenvironment is composed of cellular and non-cellular components. The cellular components mainly include immune cells (T cells, TAMs, neutrophil, NK cells, mast cells, etc.), cancer-associated fibroblasts (CAFs) and other types of cells, which activate the expression of various EMT transcriptional factors and markers by secreting cytokines and growth factors as well as regulating multiple signaling pathways, to induce EMT phenotype. Hypoxia environment as a non-cellular factor also exerts vital roles in trigger EMT by activating relevant pathways.

phenotypes (52). It has been shown that radiotherapy can change the immune statement of the tumor microenvironment. After a local irradiation, the neutrophils can infiltrate into the tumor issue and alter irradiation response (115). Neutrophils function as a promoter in lung cancer progression. Neutrophils contribute to exacerbating hypoxia microenvironment and stabilizing Snail, which in turn enhances neutrophil homing and elicits partial EMT (53). Radiotherapy has been reported to enhance the cytotoxic effect of NK cells on tumor cells, as well as increase the ability of lymphocytes to translocate into tumors, while promoting cytokine production (116). However, NK cells were also found to enhance the malignancy of melanoma cells by inducing EMT-like changes, as evidenced with increased stemness and expression of EMT markers and morphologic switching, which depends on the release of IFN- $\gamma$  and TNF- $\alpha$ . And the EMT phenotype assisted melanoma cells to escape from NK-cell killing by evaluating the NN-protective HLA-I expression or decreasing tumor-recognizing activating receptors on NK cells (54). Mast cells are one type of immune cells derived from hematopoietic stem/progenitor cells and are systemically present. Irradiation contributes to differentiation of bone marrow cells into mast cells, and affected the differentiation efficiency and function of mast cells (117, 118). Mast cells can release angiogenic-mediated VEGF by mediating MMP-9 in the tumor microenvironment after low-dose radiation therapy (119). One study demonstrated that mast cells could be recruited and activated by thyroid cancer cells in the TME, and release IL-8, which leads to EMT and tumor-initiating features of cancer cells (55). As for extracellular vesicles, radiation could stimulate the release of exosomes derived from T cells in human esophageal squamous cell carcinomas. Then exosomes induced the EMT phenotype of tumor cells *via* increasing the  $\beta$ -catenin expression and activating the NF- $\kappa$ B/snail pathway (56). Additionally, extracellular vesicle (EV)-mediated estrogen receptor-binding fragment-associated antigen 9 (EBAG9) from prostate cancer, has been proved to promote EMT by interacting with TM9SF1 to upregulate the expression of vimentin and Snail2 (120).

Radiotherapy can affect the expression of extracellular matrix components and ECM remodeling (113, 121). For instance, CAF activation following radiation leads to the secretion of numerous ECM proteins (113). Upregulation of an ECM protein SPARC could induce the occurrence of EMT in breast cancer cells, and leads to the TME reconstitution with increased infiltration of Tregs, mast cells, and MDSCs. SPARC-induced EMT was significantly correlated with MDSCs. The EMT program of cancer cells may be reverted by inhibition of suppressive function in MDSCs (122). Study found that fractionated irradiation had little effect on the morphology and capacity to contract collagen gels of CAFs, and it weakened growth and stimulated DNA-damage response of CAFs. Irradiated CAFs promoted survival of colorectal cancer (CRC) cells, and a metabolic switch favoring glutamine consumption *via* IGF-1 receptor activation (123). CAFs contribute to the gain of EMT phenotype of tumor cells, endowing them with enhanced therapeutic resistance and metastatic property (124). It has been confirmed that CAFs can induce EMT through paracrine TGF- $\beta$  to provoke the aggressive phenotype of cancer cells (57). Additionally, CAFs can produce a lot of cytokines and growth factors, such as IL-6,

EGF, VEGF and HGF, to mediate EMT (57–60). Furthermore, co-culture of esophageal cancer cells with irradiated fibroblasts provoked the cancer cells undergoing the EMT program, and increased the expression of HDGF, which are the identified mechanisms of tumor radioresistance (125).

The hypoxic microenvironment has been identified as one of the most important factors in eliciting EMT that mainly acts through hypoxia inducible factors (HIFs). Under hypoxic circumstances, the TGF- $\beta$ , NF- $\kappa$ B and Notch signaling pathways that directly trigger EMT are activated (61, 62). HIF-1 $\alpha$  is implicated in the regulation of transcription factors such as Zeb1, Snail, Twist, and promote the EMT process (63). They et al. (1) uncovered that upon hypoxia, TGF- $\beta$  addition or EGFRvIII expression, promoted the breast cancer and LC cells to acquire EMT-like phenotype, accompanied by the decreased expression of epithelial markers such as E-cadherin and increased expression of mesenchymal markers such as vimentin and N-cadherin. Intriguingly, the treatment of reoxygenation could reverse the E-cadherin expression and the mesenchymal phenotype, and mesenchymal conversion and E-cadherin loss were associated with resistance of tumor cells to irradiation. The development of EMT is a comprehensive network involving transcription, post-transcriptional regulation and cytokines from the surrounding environment. TME plays an important role in EMT and is one of the key factors in EMT-mediated radioresistance.

### 3 IRRADIATION-MEDIATED EMT PROGRAM

There is an interactive network between EMT and irradiation. The processes of EMT induces radioresistance of tumors, and irradiation further enhances EMT, providing a positive feedback loop to increase the radioresistance. After several hour's irradiation to cancer cells with X-rays, the migration and invasion capacities of these cells were increased, paralleled by a decrease of E-cadherin expression and an increase of Vimentin and Smad3 expression (126). Tsukamoto H et al. (127) also found that irradiation facilitated the migration and invasion of endometrial cancer cells by inducing the development of EMT *in vitro*.

In tumorigenesis and development, a variety of signaling pathways are significantly activated, such as MAPK/ERK, TGF $\beta$ , HIF-1, Wnt and Notch pathways, and irradiation will further activate these pathways to induce the tumor malignant phenotypes such as EMT, leading to the occurrence of radioresistance. Irradiation can increase the release of the reactive oxygen species (ROS), resulting in the activation of signaling pathways and alterations in the tumor microenvironment. ROS has been reported to be involved in irradiation-induced EMT by regulation of multiple EMT markers and transcriptional factors (128). Evaluated levels of ROS may contribute to activating NF- $\kappa$ B signaling, which increases IL-6 production by cancer cells and CAFs, thus facilitating the EMT program by regulating the expression of N-cadherin, E-cadherin, vimentin, Twist and Snail (129). In addition, irradiation could promote the upregulation of Snail *via* activating the ERK signaling and inhibiting glycogen

synthase kinase 3 $\beta$  (GSK3 $\beta$ ) (130, 131). Elimination of ROS using a ROS scavenger N-acetyl-L-cysteine (LNAC), suppressed the expression of vimentin, indicative of a vital role for ROS in irradiation-induced EMT (132).

P38 mitogen-activated protein kinase (p38MAPK) pathway was activated after irradiation, which contributes to the occurrence of EMT and invasion through increased expression of Snail (133). HIF-1 was also implicated in irradiation-induced EMT. Irradiation could increase the protein stability of HIF-1 $\alpha$  under hypoxia, and then HIF-1 $\alpha$  translocated to the nucleus, dimerized with HIF-1 $\beta$ , and regulated the gene expression of key EMT transcriptional factors, thereby inducing EMT, migration and invasion (134). Furthermore, irradiation could activate Wnt signaling pathway by mediating Wnt ligand expression, increasing  $\beta$ -catenin stabilization and transcriptional activities (70, 128, 135), which strengthens the expression of Snail to trigger EMT (71). Exposure to irradiation can promote the activation of the TGF- $\beta$  signaling, leading to the EMT in many types of cancer cells (9, 136, 137). Disturbance of TGF- $\beta$  pathway could increase the radiosensitivity *via* repressing EMT (10). Moreover, another study discovered that EMT induced by irradiation through TGF- $\beta$  pathway was not limited to the radiation dose range, and both low- and high-level radiation could contribute to the induction of EMT (138). Likewise, Zhou Y C et al. (139) irradiated six cancer cells lines with 2Gy dose, and they found that the irradiated cancer cells presented enhanced invasion and metastatic abilities, which is associated with irradiated-induced EMT process by activating TGF- $\beta$  signaling to regulate the expression of epithelial and mesenchymal markers. Li T et al. (140) demonstrated that irradiation strengthened the expression of TMPRSS4, and subsequently weakened the expression of E-cadherin, which triggers EMT to enhance the invasion and metastasis of cancer cells. Additionally, NF- $\kappa$ B pathway was activated by irradiation in A549 cells, involved in the induction of EMT (141). NF- $\kappa$ B could elicit STAT3 activation by transcriptional upregulation of HER2 expression after exposure to ionizing radiation, thus resulting in EMT-mediated radioresistance in breast cancer stem cells (142–144). Besides, evidence from another study of breast cancer uncovered that Notch signaling was highly activated in fractionally irradiated cancer cells, accompanied with the alteration of EMT phenotype. Afterward, it revealed that Notch provoked the EMT by regulating IL-6/JAK/STAT6 signaling pathway in response to fractionated-radiation (145).

Taken together, multiple signaling pathways such as Wnt, TGF- $\beta$ , NF- $\kappa$ B, Notch and HIF-1 pathways play a crucial role in the occurrence of radiotherapy-induced EMT. Meanwhile, the alterations in TME induced by radiotherapy such as increase of ROS may acts as a stimulator to involve in the activation of signaling pathways.

## 4 PERSPECTIVES ON CANCER TREATMENT

From the primary cancer to adjacent and distant organs, EMT confers the potential of tumor invasion and metastasis, as well as the capacity of inducing therapeutic resistance. Therefore, targeting

EMT by attenuating the mesenchymal/CSC phenotypes, inhibiting EMT-related signaling pathways, and perturbing tumorigenic TME, will be considered as promising therapeutic strategies for tumor treatment. The studies of these therapeutic strategies are summarized in **Table 2**.

Previous studies have verified that CSC traits are associated with mesenchymal phenotype, metastatic capacity and therapy resistance. Targeting the CSC phenotype was conducive to the acquisition of considerable therapeutic benefit (165). The ionophore salinomycin is confirmed to be 100-fold more active against CSCs than traditional chemotherapy agent paclitaxel in breast cancer (146). Notably, the treatment of tumors with salinomycin significantly reduced the tumor size compared with the control group (147).

Given the important role of signaling pathways in mediating EMT, it is promising to acquire radiosensitization by combining the inhibitors targeted against these pathways with radiotherapy. Oncomodulin M (OSM) is a member of the IL6 cytokine family, which has been identified as an important driver of mesenchymal and CSC phenotypes. Inhibition of JAK1/2 by ruxolitinib blocked the STAT3-mediated transcription of OSM receptors Zeb1 and Snail and disturbed the emergence of CSC phenotype in pancreatic ductal adenocarcinoma cells (148). Inhibition of the PI3K/Akt pathway has been proven to be an effective way to increase the sensitivity of cancer cells to radiotherapy. Chang et al. reported that application of PI3K/Akt/mTOR pathway inhibitor (BEZ235) in combination with RT could significantly weaken radioresistance by decreasing the expression of EMT/CSC markers (17). Simvastatin, a conventional drug that is utilized for cardiovascular diseases, has been reported to promote the radiosensitivity of esophageal cancer cells by suppressing PTEN-PI3K/Akt pathway (149). In preclinical models, a dual PI3K/mTOR inhibitor PF-05212384 effectively inhibited PI3K and mTOR, leading to increased sensitivity of HNSCC to radiation (150). Another Akt/mTOR inhibitor Everolimus (also known as Rad001) are currently undergoing clinical trials in combination with radiotherapy in a variety of tumors, and may become a useful method of radiosensitization (151–153). Additionally, Nimotuzumab, an anti-EGFR monoclonal antibody, exerts effective roles in improving the radioresistance of esophageal cancer KYSE-150R cells by inhibiting EGFR signaling pathway and DNA repair (154). Also, Cetuximab, another anti-EGFR pathway antibody, displays potential antitumor effect in combination with radiotherapy, and obtained a survival benefit of 10% in patients with head and neck squamous cell carcinoma (HNSCC) in a phase 3 clinical trial (155). Several types of Notch pathway inhibitors are in clinical development, especially  $\gamma$ -secretase inhibitors (GSIs), which disturb the proteolytic cleavage of Notch receptors and block the release of the active intracellular domain (NICD). In multiple preclinical models, these inhibitors have displayed significant anti-tumor activity. Noteworthy, GSI (RO4929097) in combination with RT has entered clinical trials in patients with gliomas (NCT0119599) or brain metastases (NCT01217411) (156). In gastric cancer (GC), tangeretin that acts as a Notch-1 inhibitor could enhance the radiosensitivity and counteract irradiation-induced EMT both *in vitro* and *in vivo* (157). Blockage of Notch signaling by rhamnetin

**TABLE 2** | Novel strategies targeting EMT-induced radioresistance.

Therapy	Target	Function	Reference
Ionophore salinomycin	CSC	Inhibition CSC phenotype	(146, 147)
Ruxolitinib	JAK1/2	Block the STAT3-mediated transcription of Zeb1 and Snai1, and disturb the CSC phenotype	(148)
BEZ235	PI3K/Akt/mTOR	Decrease the expression of EMT/CSC markers	(17)
Simvastatin	PI3K/Akt	Suppress PTEN-PI3K/Akt pathway and promote the radiosensitivity	(149)
PF-05212384	PI3K/mTOR	Inhibit PI3K and mTOR and increase radiosensitivity	(150)
Everolimus	Akt/mTOR	Inhibit Akt/mTOR pathway	(151–153)
Nimotuzumab	EGFR	Weaken radioresistance by inhibiting EGFR signaling pathway and DNA repair	(154)
Cetuximab	EGFR	Increase the radiosensitivity	(155)
GSI (RO4929097)	Notch	Suppress Notch signaling	(156)
Tangeretin	Notch	Enhance the radiosensitivity and counteract irradiation-induced EMT	(157)
Rhannetin and cirsiolol	Notch	Reverse EMT phenotype and improve radiosensitivity	(24)
FH535	$\beta$ -Catenin/Tcf	Inhibit the activation of Wnt/ $\beta$ -catenin pathway and increasing E-cadherin expression	(13)
Sunitinib	Hypoxia	Reduce tumor hypoxia and angiogenesis, and radiosensitize cancer stem-like cells	(158)
Paclitaxel	Hypoxia	Overcome HIF-1 $\alpha$ -induced radioresistance	(159)
Sorafenib	Hypoxia	Suppress HIF-1 $\alpha$ expression	(160)
Bortezomib	Hypoxia	Suppress HIF-1 $\alpha$ expression	(161)
Albumin–MnO <sub>2</sub> nanoparticles	Hypoxia	Improve hypoxic environment, and strengthen the radiosensitivity	(162)
Acriflavine	HIF1	Suppress HIF1 dimerization and transcriptional activity	(163)
YC-1	HIF1	Inhibit HIF1 and enhance radiosensitivity	(164)

and cirsiolol could result in the reversal of EMT phenotype and improvement of radiosensitivity in NSCLC (24). These findings implied that inhibiting EMT by blockage of the Notch pathway may be an effective means to reduce EMT-mediated radioresistance. Wnt pathway plays a protective role for cancer cells in response to IR, therefore, targeting the Wnt signaling may also be important for enhancing radiosensitization. FH535, a  $\beta$ -Catenin/Tcf inhibitor that can inhibit the activation of Wnt/ $\beta$ -catenin pathway, is known as a potential radiosensitizer. It could effectively suppress EMT to reverse the radioresistance of KYSE-150R cells by increasing E-cadherin expression (13). Other small molecule inhibitors have been used in preclinical trials or clinical trials and shown good efficacy in blocking the Wnt signaling pathway (156, 166–168). Currently, several HIF-1-targeting agents have been applied in clinical practice, such as sunitinib (158), paclitaxel (159), sorafenib (160) and bortezomib (161). These agents, as antineoplastic chemotherapy or targeted treatment, can be combined with radiotherapy to play the role of radiosensitization. Furthermore, with the rapid development of nanotechnology, the method generating oxygen in hypoxic tumor regions has been accomplished by intratumoral injection of albumin–MnO<sub>2</sub> nanoparticles, which will conduce to the improvement of hypoxic environment and strengthen the radiosensitivity (162). Acriflavine has been revealed that could suppress HIF1 dimerization and transcriptional regulation *via* directly binding to the HIF1 $\alpha$  subunit (163). The application of YC-1, a HIF1 inhibitor, also displayed the treatment benefits when administered after irradiation (164).

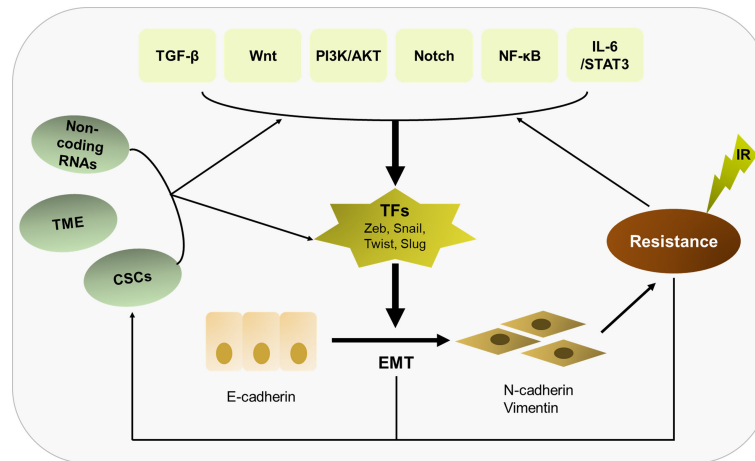
In addition to the agents mentioned above, there are several old drugs that also have potential radiosensitizing effects. The anti-diabetic drug metformin can suppress the EMT program and stemness by regulating transcriptional reprogramming and inhibiting ZEB1, TWIST1 and SLUG (169, 170), and strengthens the sensitivity of cancer cells to irradiation (171). Berberine could reduce the expression of vimentin and evaluate the level of E-cadherin, thereby perturbing the TGF- $\beta$ -induced EMT and sensitizing nasopharyngeal carcinoma cells to radiation (10).

Although many agents exhibited effective roles in radiosensitization, they are rarely applied in clinical practice as radiosensitizers. We consider the possible reasons for blocking the transformation of these agents as follows. First, the efficacy of many agents is verified *in vitro* experiments or in preclinical animal experiments, however, no good therapeutic effects is observed in clinical trials. Second, the limitation of transformation may be partly attributed to safety of the agents. Combined application of the agents with radiotherapy may amplify adverse reactions, even leading to some serious complications, which is an important reason for restricting the clinical application of many agents. Third, the molecular mechanisms involved in EMT are extremely complex, and these factors do not operate isolation, but functions as a coordinated signaling network, ultimately leading to the output of EMT program. Therefore, a comprehensive understanding aiming to the key nodes in this network is needed for the development of EMT-targeting radiosensitizers, which increases the difficulty of drug transformation. Last, drug delivery into cancer cells is also an important factor that needs to be solved urgently. Drug transport into malignant tumors through blood relies on a variety of factors, and is affected by tumor vascular system and tissue characteristics. Moreover, irradiation has a significant impact on the revascularization of tumor tissues, so how to increase the drug concentration at the tumor site may also be a factor that limits the radiosensitivity. Currently, the application of microcarriers based on nanoparticles or liposomes may provide a potential method to improve the tumor-killing effect and increase the sensitivity of radiotherapy.

## 5 CONCLUSIONS

In summary, radioresistance is still regarded as a major challenge in current tumor treatment, and EMT as an important inducer of





**FIGURE 3** | Overview of the relationship of EMT with radioresistance and their crosslinked mechanisms. EMT plays a central role in eliciting radioresistance. Multiple molecular mechanisms are involved in EMT-induced radioresistance, including TGF- $\beta$ , Wnt, PI3K/AKT, Notch, NF- $\kappa$ B, IL-6/STAT3, non-coding RNAs, CSCs and tumor microenvironment. Besides, there is a vicious circle between EMT and irradiation. Irradiation can further enhance the EMT program, thus strengthening radioresistance.

radioresistance has attracted large amount of attention. In this review, we hold the opinion that EMT is not only the cause to induce radioresistance, but the result of irradiation acting on cancer cells and TMEs, thus forming an infinitely amplified positive feedback network to further increase the resistance of tumor cells to radiotherapy (Figure 3). We must comprehensively recognize that EMT plays a central role in eliciting resistance of tumor cells to radiotherapy, involved in multiple molecular mechanisms including signaling pathways, non-coding RNAs, CSCs and tumor microenvironment. The fact that there is a vicious circle between EMT and irradiation needs to be better understood. At the present, there are an array of agents in preclinical or clinical trials that work on EMT or its related signal pathways. Based on continuous progression on molecular medicine and novel biotechnology, it holds promise in overcoming radioresistance and improving the prognosis of cancer patients.

## AUTHOR CONTRIBUTIONS

JZ and LQ conceived the framework of manuscript. LQ and YC were responsible for writing the manuscript. NL, YL, JX and XW conducted the figure and tables. FL, GD, and FC performed the revision of the manuscript. All authors have read and approved the final manuscript.

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