Research Progress on Long Non-Coding RNA and Radiotherapy

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCEFG 1,2 **Zhifeng Yao***
ABCDEF 3 **Yiwen Zhang***
ABC 4 **Danghui Xu**
ABDE 5 **Xuejun Zhou**
DEF 6 **Peng Peng**
ABDE 7 **Zhiyao Pan**
CDEF 8 **Nan Xiao**
DEF 8 **Jianxin Yao**
ABCDEFG 8 **Zhanfeng Li**

1 Department of Radiotherapy, The Second Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu, P.R. China
2 Department of Oncology, The Second Clinical Medical School of Nanjing Medical University, Nanjing, Jiangsu, P.R. China
3 Department of Nursing, The Affiliated Children's Hospital of Nanjing Medical University, Nanjing, Jiangsu, P.R. China
4 Department of Medical Imaging, Jiangsu Provincial Hospital of Traditional Chinese Medicine, Nanjing, Jiangsu, P.R. China
5 Department of Medical Imaging, The Affiliated Hospital of Nantong University, Nantong, Jiangsu, P.R. China
6 Department of Nursing, Nanjing Health Higher Vocational and Technical College, Nanjing, Jiangsu, P.R. China
7 Department of Basic Medicine, Zhejiang University Medical College, Hangzhou, Zhejiang, P.R. China
8 Department of Medical Imaging, Nanjing Health Higher Vocational and Technical College, Nanjing, Jiangsu, P.R. China

* Zhifeng Yao and Yiwen Zhang equally contributed to this article
Corresponding Authors: Zhifeng Yao, e-mail: yzf058565@126.com, Zhanfeng Li, e-mail: pycyzf@163.com
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Long non-coding RNAs (lncRNAs), a group of non-protein-coding RNAs longer than 200 nucleotides, are involved in multiple biological and pathological processes, such as proliferation, apoptosis, migration, invasion, angiogenesis, and immune escape. Many studies have shown that lncRNAs participate in the complex network of cancer and play vital roles as oncogenes or tumor-suppressor genes in a variety of cancers. Moreover, recent research has shown that abnormal expression of lncRNAs in malignant tumor cells before and after radiotherapy may participate in the progression of cancers and affect the radiation sensitivity of malignant tumor cells mediated by specific signaling pathways or cell cycle regulation. In this review, we summarize the published studies on lncRNAs in radiotherapy regarding the biological function and mechanism of human cancers, including esophageal cancer, pancreatic cancers, nasopharyngeal carcinoma, hepatocellular carcinoma, cervical cancer, colorectal cancer, and gastric cancer.

MeSH Keywords: **Cell Line, Tumor • Radiation-Sensitizing Agents • RNA, Long Noncoding**

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Background

Malignant tumors, a type of disease that seriously threatens humans, is one of the major causes of death all over the world. In recent years, both the morbidity and the mortality have increased significantly. According to mortality data collected by the National Center for Health Statistics, it is estimated that 1 762 450 new cancer cases and 606 880 cancer deaths are projected to occur in the United States in 2019 [1]. Radiotherapy combined with chemotherapy is a standard treatment for advanced malignant tumors. However, even at the same stage and pathological grade, the efficacy of radiotherapy of malignant tumors differs widely. Some patients will have recurrence, metastasis, and obvious radiotherapy resistance [2]. Radiotherapy is a routine treatment for malignant tumors. The latest data show that radiotherapy in the course of disease is required for 30~50% of all cancer patients. The sensitivity of radiotherapy is the key to the curative effect of malignant tumors, and its target is DNA. After DNA damage, cells initiate repair systems to repair DNA damage to a certain extent, resulting in reduced radiosensitivity and increased radiotherapy resistance, which affects the therapeutic effect. Radiotherapy is effective against malignant tumors, with high sensitivity, but not all malignant tumors have good radiotherapy effects, because certain kinds of tumors are not sensitive to radiotherapy, for the reason that some patients cannot benefit from it. With the deepening of research, it has been found that radiosensitivity is closely related to cell hypoxia, cell cycle, proliferative activity, DNA damage repair, and cell apoptosis. The nature of radiosensitivity is the biological response of related genes to radiation [3]. It is believed that radiotherapy resistance may be associated with multiple biological pathways which are activated in the hypoxic region of the tumor, thus protecting tumor cells from radiation damage [4,5]. The radiotherapy resistance may also be related to DNA damage and repaired gene mutation [6,7], occur in connection with the activation of intracellular pro-survival signaling pathways [8–10], or with effects on cell cycle regulation or inhibition of apoptosis [11,12].

Long non-coding RNAs (lncRNAs) are abnormally expressed in a variety of cancers and play a vital role in the regulation of diverse biological processes such as proliferation, apoptosis, migration, invasion, angiogenesis, abnormal metabolism, and immune escape [13–16]. Some studies have focused on analyzing molecular mechanisms and networks, aiming to expose their role in the development of cancer [15,16]. In recent years, increasing evidence demonstrates that lncRNAs are associated with the radiosensitivity of malignant tumors [17,18]. This article reviews the research progress on lncRNAs in radiotherapy regarding their biological function and mechanism in human cancers, including esophageal cancer, nasopharyngeal carcinoma, cervical cancer, colorectal cancer, pancreatic cancer, hepatocellular carcinoma, and gastric cancer, to provide new strategies for individualized radiosensitization.

Long Non-Coding RNAs

Gene sequences can be divided into coding sequence and non-coding sequence. lncRNAs are a set of non-coding transcripts longer than 200 nucleotides [19]. Initially, it was thought that lncRNAs are transcriptional noise of encoding genes. It was found later that lncRNAs can regulate transcription through chromatin remodeling, and can also participate in post-transcriptional regulation through a variety of mechanisms, including protein complex assembly and signal transduction in cells [20], thus revealing a new non-traditional genetic information expression and regulation network mediated by lncRNAs [21].

The classification of lncRNAs is diverse and can be divided into 5 categories according to relationship with the location of the coding gene: (1) Sense strand, which overlaps one or more exons with another coding gene on the same strand; (2) Antisense strand, which overlaps one or more exons with another coding gene on the opposite strand; (3) Bidirectional strand, which is very close to the transcriptional start site of coding genes located on opposite strand, but the transcriptional direction is opposite; (4) It is located in the intron region and originates from the intron region of the secondary transcript (sometimes the precursor sequence of the mRNA); and (5) It is located in the gene interval region, which is the region between the 2 genes [22]. lncRNAs can also be classified into 4 categories according to mechanism: (1) as a signaling molecule, it transmits information through signaling pathways; (2) as a guiding signal, it recruits chromatin-modifying enzymes to localize the protein complex in cis or trans regulatory sites, (3) as an inducible molecule, which indirectly regulates the transcription of target genes; and (4) as a scaffold, which regulates target genes by histone modifications at the epigenetic level [23].

lncRNAs directly regulate transcription and translation of target genes in various ways or indirectly regulate upstream or downstream genes of target genes [24]. lncRNA is involved in several cell life activities, such as gene imprinting, gene recombination, chromatin modification, cell cycle regulation, transcription, and translation [25–29]. Recent studies suggest that lncRNAs play a regulatory role in gene expression at 3 levels: epigenetics, transcription, and post-transcriptional processing. Abnormal expression of lncRNAs occurs during the initiation and development of various malignant tumors. The lncRNAs expression in human tumors was first discovered in breast cancer [30]. The expression of lncRNA HOX transcription antisense RNA (HOTAIR) in primary breast cancer and metastatic cancer was increased, and tumor metastasis and prognosis can be

predicted through the expression in primary tumors. Studies have shown that the expression of lncRNA-HULC is highly specific in hepatoma. Yang et al. applied real-time quantitative PCR to detect H19 in gastric cancer tissues, showing that the expression of H19 was significantly increased in gastric cancer tissues and cells compared with that of a normal control group, and the excessive expression of H19 could promote cell proliferation, while H19 expression by siRNA interference could induce apoptosis in gastric cancer cells [31].

Radiotherapy and Radiation Sensitivity

In recent years, various new technologies have pushed radiotherapy toward the era of precise radiotherapy characterized by precise positioning, precise planning, and precise treatment. Representative technologies include bio-guided radiotherapy, image-guided radiotherapy, dose-guided radiotherapy, 3D conformal radiotherapy, intensity-modulated radiotherapy, proton radiotherapy, and heavy ion radiotherapy. The principle of radiotherapy is to stimulate DNA damage, inhibit cell proliferation, and induce cell apoptosis by radiation. At the same time, it can activate several signal pathways in tumor cells, including tyrosine kinase receptor signal pathways such as EGFR-Ras-Raf-MAPK and PI3K/AKT, so as to regulate gene expression [32]. Radiotherapy can also change the radiosensitivity of tumor cells by activating transcription factor, upregulating chemokine receptor, and upregulating cytokine [33]. Radiation also acts on the plasma membrane and subcellular organelles, thereby regulating cell biological behavior [34]. The radiated tumor cells can transmit bystander response signals to kill adjacent tumor cells and protect normal tissues from damage [35].

The "4R" radiobiology theory proposed by Withers – repair of sublethal damage, redistribution of cell cycle phase, re-proliferation and re-oxygenation – is the biological basis of clinical fractional radiotherapy [36]. The following is a review of the 4R theory's perspective on factors affecting radiosensitivity.

Repair of Sublethal Damage

The high-energy radiation used in clinical practice enters the cells and interacts with water molecules to produce reactive oxygen species (ROS), which damage DNA [37]. Studies have shown that cancer stem cells (CSCs) are more radioresistant than are non-cancer stem cells. CSCs have strong ROS scavenging ability, which reduces ROS levels, resulting in less initial DNA damage than with non-CSCs [38]. CSCs produce less γ-H2AX after exposure, suggesting that the DNA repair ability of CSCs is significantly stronger than that of non-CSCs [39]. Further studies have found that CSCs can promote the phosphorylation of DNA checkpoint kinases Chkl and Chk2 more

effectively, thereby making repair of DNA double-strand break faster than that with non-CSCs [40].

Redistribution of Cell Cycle Phase

Cells at different phases of the cell cycle have different radiosensitivities, and the cells at G_0 phase are most resistant to radiation. Recent studies have shown that cells at G_0 phase have the characteristics of steady-state CSCs [38]. When the tumor cells are radiated, those that are in the cell cycle and are sensitive to radiation are killed, which activates the Notch signaling pathway, thereby promoting the entry of CSCs into the cell cycle and increasing the proportion of cells in the cell cycle, as well as accelerating cell cycle phase redistribution [41].

Repopulation

Early studies have shown that tumor cells accelerated repopulation in the course of 6~7 weeks of clinical radiotherapy, which may be an important reason for the failure of conventional radiotherapy. CSCs also play an important role in cell repopulation. Radiation of tumor cells activates the Notch signaling pathway, allowing CSCs to maintain their stem cell phenotype [42]. At the same time, radiation-sensitive non-CSCs produce highly expressed TGF-β upon exposure to radiation, which antagonizes the proliferative effects of CSCs triggered by the Notch signaling pathway. During fractionated radiation therapy, the radiation-sensitive non-CSCs are killed and the expression of TGF-β is decreased with the increase of radiation dose, so that the antagonism of Notch is weakened, which causes the tumor cells to accelerate repopulation [43].

Re-Oxygenation

Due to the imbalance of oxygen supply and demand, most of the solid tumor microenvironment has hypoxia, and hypoxic tumor cells are less radiosensitive than oxygen-rich tumor cells, which are more resistant to radiation. Therefore, when the oxygen-rich tumor cells are killed by radiation in the process of fractionated radiotherapy, the original hypoxic tumor cells are re-oxygenated due to the shrinkage of the tumor volume and the redistribution of the tumor blood vessels, thereby achieving self-radiation sensitization. CSCs located around the vessel are close to the vessel, so these cells are relatively oxygen-rich, and most of them are relatively sensitive to radiation; these are called activated CSCs. CSCs located around the non-vascular tube are relatively hypoxic due to their distance from the vessel, and most of them are in G_0 phase, which is relatively resistant to radiation. These CSCs are known as steady-state CSCs [38]. During fractionated radiotherapy,

relatively oxygen-rich activated CSCs are killed after radiation, and then the relatively hypoxic-surviving steady-state CSCs gradually transform into activated CSCs by improving the degree of hypoxia, and are more likely to be killed in re-radiation, thereby achieving the self-sensitization effect of fractionated radiotherapy [43].

Long Non-Coding RNAs and Radiotherapy

The DNA damage response involves complex detection and repairing damaged networks, in which lncRNA, as a new regulatory RNA, may play an important role. Wan et al. confirmed that after DNA damage, the expression of transcription factor E2F1 was promoted in an ataxia-telangiectasia mutant (ATM)-dependent manner, and then the transcription of ANRIL was upregulated by p53-independent regulation. The expression of ANRIL was increased, thus the expression of INK4a, INK4b, and ARF were inhibited in the late stage of DNA damage response, making the cells recover to normal when DNA repair is complete. Through DNA damage caused by neocarcinogenin (NCS) in the DNA damage response process, ANRIL can promote cell proliferation and DNA synthesis, as well as inhibiting cell apoptosis and cell cycle checkpoint, resulting in increased numbers of S-phase cells and decreased numbers of G_1 phase cells to promote cell cycle progression. The homologous recombination repair produces functional GFP by importing defect GFP, and silencing the expression of ANRIL reduced homologous recombination repair by 50%, thus we speculated ANRIL is necessary to the homologous recombination pathway [44].

Zhang et al. explored the expression of lncRNA LINP1, which is closely related to tri-negative breast cancer [45]. LINP1 links between Ku80 and DNA-PKcs like a scaffold, which is critical to of repair non-Homologous End Joining (NHEJ) in DNA double-strand breaks, and can enhance NHEJ repair [46–49]. When DNA double-strands break, ku80-ku70 heterodimers recruit LINP1 to DNA lesion sites, forming the Ku80 and DNA-PKcs complex, which enhances the NHEJ repair of DNA. Activated EGFR upregulates LINP1 expression and enhances NHEJ repair through the RAS-MEK-ERK signaling pathway and AP1 transcription, while p53 downregulates the expression of LINP1 through miR-29 targeting. However, the feedback regulation is slow. It is speculated that this negative feedback regulation mechanism restricts NHEJ repair, mainly after DNA damage, for a long time. Sharma et al. found that lncRNA DDSR1 was induced in an ATM-NF-κB-dependent manner during DNA damage and they explored the relationship between DDSR1 and homologous recombination repair [50]. DDSR1 expression was found to be downregulated by increasing BRCA1 and RAP80 recruitment, resulting in reduced homologous recombination. In the early stages of DNA double-strand rupture, BRCA1 recruitment promotes homologous recombination repair, whereas

the complexes formed by BRCA1 and RAP80 limit homologous terminal repair by inhibiting terminal resection of DNA double-strand breaks [51–53]. It was further suggested that DDSR1 and hnRNPUL1 together recruit BRCA1 and RAP80 to regulate homologous recombinant repair at DNA double-strand breaks.

DNA damage response is an important anti-tumor disorder, which maintains genome integrity, protects against ultraviolet, radiotherapy, and chemotherapy damage, oncogenic damage, and internal and external genetic toxicity, including ROS. In view of the above research, lncRNAs are predicted to affect the sensitivity of radiotherapy and may also play an important regulatory role in radiotherapy.

LncRNAs in Radiotherapy of Various Cancers

Different lncRNAs have different effects on radiation sensitivity of different malignant tumors. Here, we provide some examples from esophageal cancer, nasopharyngeal carcinoma, cervical cancer, colorectal cancer, pancreatic cancer, hepatocellular carcinoma, and gastric cancer. In this review, we illustrate the effect of lncRNA on the radiosensitivity of cancer and the underlying mechanisms (Table 1).

Esophageal Cancer

Globally, esophageal cancer (EC) is one of the most common types of cancer, with the 7th highest incidence rate and 6th highest rate of cancer-associated death [54]. Surgery still plays an important role in the treatment of EC. However, studies have shown that only 25% of newly diagnosed patients are suitable for surgery due to tumor pathology, location, or stage [55]. For patients with unresectable EC, radiotherapy is now one of the most important, effective, and safe treatment methods for EC. However, predominantly because of local failure associated with intrinsic and/or acquired radioresistance, the survival rate in EC patients following radiotherapy is as low as 10~30% after 5 years [56]. Therefore, knowing how to predict the radiosensitivity and develop new strategies for radiosensitization is urgent for EC patients receiving radiotherapy.

Recent research has reported that lncRNAs also function as regulators of radiosensitivity and may serve as biomarkers for tumor response to radiotherapy [57]. However, radiosensitivity-associated lncRNAs in esophageal squamous cell carcinoma (ESCC) are rarely reported [58–61]. Tong et al. conducted the earliest study on lncRNAs associated with radiosensitivity in ESCC in 2014; they showed that tumor tissues had a relatively low expression of LOC285194 and displayed a larger tumor size, an advanced tumor TNM stage, a poorer histological grade, and more lymph node and distant metastases compared with

Table 1. The functional role of lncRNAs in cancers related to radiotherapy.

Cancer type	lncRNA	Expression	Role	Effects	Related molecules	Ref.
Esophageal cancer	LOC285194	Downregulated	Anti-oncogene	Proliferation, apoptosis	P53	[58]
	MALAT1	Upregulated	Oncogene	Proliferation, apoptosis	cks1	[63]
	BOKAS	Upregulated	Oncogene	Proliferation, apoptosis,	WISP1 cytochrome C, Bcl-xl, γ-H2AX, PI3K kinase	[64]
	AFAP-AS1	Upregulated	Oncogene	Proliferation, apoptosis, EMT	SPRY4-IT1	[65]
	HOTAIR	Upregulated	Oncogene	Proliferation, apoptosis, EMT	Snail, β-catenin, E-cadherin	[77]
	FAM201A	Upregulated	Oncogene	Proliferation, apoptosis	miR-101, ATM, mTOR	[78]
Nasopharyngeal carcinoma	XIST	Upregulated	Oncogene	Proliferation, apoptosis	miR-29c	[84]
	MALAT1	Upregulated	Oncogene	Proliferation, apoptosis	miRNAs-1, Slug	[85]
	ANRIL	Upregulated	Oncogene	Proliferation, apoptosis	miR-125a	[86]
Cervical cancer	HOTAIR	Upregulated	Oncogene	Proliferation, cell cycle	p21, Ki-67	[89]
	MALAT1	Upregulated	Oncogene	Proliferation, apoptosis, cell cycle	miR-145 cyclin D1, cyclin E, CDK6 miR-143	[90-92]
	GAS5	Upregulated	Oncogene	Apoptosis, cell cycle	IER3, miR-106b	[95]
	NEAT1	Upregulated	Oncogene	Proliferation, cell cycle, apoptosis	miR-193b-3p, cyclin D1	[96]
Colorectal cancer	lincRNA-p21	Upregulated	Oncogene	Apoptosis	Wnt/β-catenin Noxa	[98,99]
	OIP5-AS1	Upregulated	Oncogene	Cell cycle, apoptosis	miR-369-3p, DYRK1A	[103]
	UCA1	Upregulated	Oncogene	Proliferation, cell cycle, apoptosis, EMT		[104]
Pancreatic cancer	HOTAIR	Upregulated	Oncogene	Proliferation, apoptosis, EMT, autophagy	WIF1, Wnt/β-catenin, ATG7	[105,106]
	LINC00673	Downregulated	Anti-oncogene	Proliferation, cell cycle, ubiquitination	PTPN11, SRC-ERK, STAT1, PRPF19	[110]

Table 1 continued. The functional role of lncRNAs in cancers related to radiotherapy .

Cancer type	lncRNA	Expression	Role	Effects	Related molecules	Ref.
Gastric cancer	lincRNA-p21	Upregulated	Oncogene	Proliferation, cell cycle, migration	Wnt/β-catenin, c-myc	[113]
	Linc00673	Upregulated	Oncogene	Proliferation, apoptosis	EZH2, LSD1, KLF2, LATS2	[114]
	TINCR	Upregulated	Oncogene	Proliferation, apoptosis, cell cycle	KLF2, p21, p15	[115]
	HOTAIR	Upregulated	Oncogene	Proliferation, apoptosis, EMT	miR-31-3p, HER2/AKT/HSF-1/Slug	[117]
Hepatocellular carcinoma	TUG1	Upregulated	Oncogene	Proliferation, apoptosis	PRC2, KLF2	[120]
	XIST	Upregulated	Oncogene	Proliferation, apoptosis, cell cycle, invasion, metastasis	PTEN, miRNA-181a, PIP3, AKT	[125, 126]
	H19	Upregulated	Oncogene	Proliferation	miR-193a-3p, PSEN1	[130]

normal adjacent tissue, and was significantly negatively correlated with the pathological response to radiotherapy, in contrast to the LOC285194-high group [58]. Low LOC285194 expression has been reported to induce radioresistance in EC patients [59–61]. Interaction of tumor-suppressor genes *p53* and *p53* response factors upstream can induce LOC285194 transcription [62]. The mutation or deletion of *p53* may lead to EC, so the effect of LOC285194 on radiotherapy can be achieved by *p53*. This suggests lncRNAs not only induces radiation resistance, but also enhances the sensitivity of radiotherapy.

Subsequently, other lncRNAs related to ESCC radiosensitivity have been screened and intensively studied, including MALAT1 [63], BOKAS [64], and AFAP1-AS1 [65].

ESCC with overexpression of MALAT1 and upregulation of cyclin-dependent kinase subunit (cks1) is radioresistant, and downregulation of MALAT1 can improve the radiotherapeutic effect of ESCC. In addition, radiotherapy can decrease the expression of MALAT1 in ESCC and decrease the expression of Cks1 [66]. Overexpression of Cks1 in breast cancer has been shown to inhibit DNA damage caused by oncogene activation [67], resulting in radiotherapy resistance. However, further studies are needed to confirm the specific regulatory mechanism of MALAT1 and Cks1 in the EC and signal pathways associated with radiotherapy.

BOKAS is another lncRNA causing radiotherapy resistance. After radiotherapy, the expression of BOKAS is upregulated, which promotes the expression of carcinoembryonic gene WISP1. WISP1 is a downstream target gene of the Wnt/β-catenin signaling pathway ad was found to be re-expressed as an oncofetal gene in 67.3% of ESCC patients. WISP1 inhibits the apoptosis of radiation-induced cells by inhibiting the expression of cytochrome c and Bcl-xl, and also inhibited the expression of γ-H2AX induced by radiation. WISP1 also repressed radiation-induced DNA damage and activated PI3K kinase, leading to radiation resistance. BOKAS was upregulated following radiation and promoted WISP1 expression and resultant radioresistance. WISP1 facilitated its own expression in response to radiation, creating a positive feedback loop and increased radioresistance. The positive feedback loop of WISP1 expression in response to radiation also enhanced radioresistance. WISP1-positive ESCC patients had significantly poorer prognosis than WISP1-negative patients after radiotherapy. Serum concentrations of WISP1 after radiotherapy are reversely correlated with relapse-free survival. Therefore, the expression of WISP1 can predict prognosis of ESCC patients treated with radiotherapy and can be used as a potential target for radiation resistance in patients with ESCC [68]. Increasing evidence has demonstrated that DNA damage response is closely associated with cell radiosensitivity [44,45]. DNA double-strand breaks (DSBs) are recognized as the main form of DNA damage induced by radiation [69]. γ-H2AX, a known marker of DSBs, is highly expressed following radiation and plays vital roles in initiating DNA damage response. WISP1 was found to inhibit radiation-induced γ-H2AX expression, leading to greatly attenuated DNA damage response and a reduced inhibitory effect of radiation on ESCC. WISP1 was found to mediate radioresistance by activation of anti-apoptotic PI3K kinase. It has been reported that PI3K kinase is associated with 3 known major radioresistance mechanisms: intrinsic radioresistance, tumor cell proliferation, and hypoxia [70]. Inhibition of PI3K kinase activity can enhance tumor radiosensitivity. PI3K kinase is a downstream effector

of WISP1 in the development of ESCC radioresistance [70–72]. However, how BOKAS promotes WISP1 expression needs to be further clarified in future work.

There are many other lncRNAs that cause radiation resistance. For example, Zhou et al. found that overexpression of lncRNA AFAP-AS1 was associated with radiotherapy resistance to ESCC [73]. SPRY4-IT1 plays an oncogene role in EC and it is associated with epithelial-mesenchymal transition (EMT) [74]. EMT refers to the acquisition of mesenchymal cell subtypes by the loss of epidermal characteristics, thus having metastasis-related invasive characteristics. EMT can induce radiotherapy resistance [75,76].

The increased expression of HOTAIR and its target factors – Snail and β-catenin – and decreased expression of E-cadherin play an important role in radiotherapy resistance, invasion, and metastasis of EC. The expression of HOTAIR- and EMT-related factors is also reduced, whereas E-cadherin expression level is high in the Eca109 cell line with relatively low expression level of HOTAIR, indicating that the radiotherapy resistance of this cell line is lower than that of other cell lines. The radioresistant cell line Eca109 R60/2 was established by fractional irradiation. The expression of HOTAIR in radiation-resistant cell line Eca109 R60/2 was significantly higher than that in Eca109, and the expression of the EMT-related factors Snail and β-catenin in the Eca109 R60/2 cell line were obviously higher than those in Eca109, while the expression of E-cadherin in Eca109 R60/2 cells was significantly decreased [77].

A family with sequence-similarity 201-member A (FAM201A) was identified as the lncRNA that contributes most to the radiosensitivity of ESCC. FAM201A is upregulated in radioresistant ESCC tumor tissues and has a poorer short-term response to radiotherapy, resulting in inferior overall survival. FAM201A knockdown enhances the radiosensitivity of ECA109/ECA109R cells by upregulating ataxia-telangiectasia-mutated (ATM) and mammalian target of rapamycin (mTOR) expression via the negative regulation of miR-101 expression. FAM201A, which mediates the radiosensitivity of ESCC by regulating ATM and mTOR expression via miR-101.FAM201A, contributes to radioresistance through a FAM201A-miR-101-ATM/mTOR regulatory network in ESCC, which may be a potential biomarker for predicting radiosensitivity and prognosis, as well as being a therapeutic target for enhancing cancer radiosensitivity in ESCC [78]. However, the upstream mechanism for FAM201A upregulation in regulating ESCC radiosensitivity needs further study.

Nasopharyngeal Carcinoma

Nasopharyngeal carcinoma (NPC), deriving from the epithelial lining of the nasopharynx, is a most common head and neck cancer [79]. NPC is highly prevalent in Southeast Asia and southern China, particularly in Guangdong province. Because NPC is sensitive to radiotherapy, radiotherapy is still the preferred treatment for NPC patients [80]. Although great advances have been made in radiation techniques, the prognosis of NPC patients remains unsatisfactory due to radioresistance. However, the precise molecular mechanisms underlying radioresistance in NPC remain largely unknown. Therefore, it is urgent to discover the molecules involved in NPC radioresistance, providing novel therapeutic targets for NPC patients.

There also have been some studies on the correlation between radiotherapy of NPC and lncRNAs. Recent research has found that XIST was upregulated in NPC cells, and radiation triggered an obvious increase in XIST expression in NPC cells. Furthermore, loss of function analysis found that XIST knockdown suppressed proliferation and improved radiosensitivity by inhibiting DNA damage repair in NPC cells. Considerable evidence suggests that lncRNAs can function as ceRNAs through sponging with miRNAs to regulate multiple mRNAs. miR-29c was reported to be downregulated and to function as a tumor-suppressor in several tumors, including NPC [81,82]. miR-29c was reported to enhance the sensitivities of human NPC to radiotherapy [83]. XIST was upregulated and miR-29c was downregulated in NPC cells. Similarly, XIST expression was increased and miR-29c expression was decreased after radiation. Another study showed that knockdown of XIST inhibited cell proliferation and increased radiosensitivity of NPC cells by upregulating miR-29c, suggesting that targeting XIST/miR-29c may be a novel strategy to improve radiotherapy for patients with NPC [84].

It was found that MALAT1 can downregulate the expression of miRNAs-1 and upregulate the level of Slug in NPC cells. Overexpression of Slug can reverse the inhibition of CSCs induced by downregulation of MALAT1 and increase the radiosensitivity. The downregulation of MALAT1 increased radiosensitivity of NPC cells. It was confirmed that Slug regulates the radiosensitivity of NPC cells by regulating the activation of CSCs. It is speculated that MALAT1 regulates the activation of CSCs and increases the radioresistance of NPC cells by regulating the expression of Slug [85].

Increasing evidence demonstrates that lncRNA ANRIL serves as a fatal oncogene in many cancers, including NPC. The expression of ANRIL was upregulated in NPC tissues and cells. Knockdown of ANRIL suppressed proliferation, promoted apoptosis, and increased radiosensitivity in NPC via functioning as a miR-125a sponge. ANRIL negatively modulates miR-125a expression. Furthermore, upregulation of ANRIL reserved the inhibited proliferation, induced apoptosis, and enhanced radiosensitivity triggered by miR-125a overexpression, suggesting that targeting the ANRIL/miR-125a axis may be a novel therapeutic application to address NPC radioresistance [86].

Cervical Cancer

Cervical cancer (CC) is the most common gynecological cancer and it seriously endangers the health and life of women. For those patients at advanced or terminal stage, radiotherapy can greatly improve the prognosis of cervical cancer, and is the most common treatment for CC [87]. However, cellular resistance to radiotherapy is the main cause of treatment failure in cervical cancer patients [88]. Some patients may present uncontrollable or recurrent cancer due to more radiation resistance and worse prognosis. Therefore, it is urgent to find new targets to improve cellular radiosensitivity in cervical cancer. In-depth investigation of the mechanisms underlying radiotherapy resistance in cervical cancer is of great importance for improving radiation sensitivity and efficacy in cervical cancer.

Studies have shown some links between CC radiotherapy and lncRNAs. Jing et al. showed that the overexpression of HOTAIR can predict the radioresistance of CC, and the overexpression of HOTAIR was negatively correlated with the level of p21. In the Hela cell line, downregulation of HOAIR expression can promote p21 expression, whereas in the C33A cell line, upregulation of HOTAIR expression can significantly inhibit p21 expression. These results suggest that downregulation of HOTAIR expression can increase G_1 phase cell distribution and significantly increase radiosensitivity of Hela cells, but this effect can be inhibited by p21 inhibitors. Compared with the parent cells, the S-phase cells increased in HOTAIR overexpressed C33A cells, accompanied by increased resistance to radiation. However, both the cell apoptosis and radiotherapy sensitivity increased after upregulation of p21 expression. Animal experiments confirmed that downregulation of HOTAIR expression inhibits tumor growth and increases tumor sensitivity to radiotherapy. Immunohistochemical staining of transplanted tumors showed that downregulation of HOTAIR expression resulted in downregulation of Ki-67 expression and upregulation of p21 expression, and it was more obvious when downregulation of HOTAIR and radiotherapy were combined. It is speculated that HOTAIR induces radiotherapy resistance by downregulating the expression of p21, and this effect can be reversed by upregulating the expression of p21 [89].

It was found that MALAT1 could alter the radiosensitivity of CC cells infected with high-risk human papillomavirus by regulating the cell cycle and (possibly) by negatively regulating the expression of miR-145 at the post-transcriptional level [90]. After radiation of CC cells, the expression of MALAT1 was upregulated and the expression of miR-145 was downregulated. After downregulated of the expression of MALAT1, the colony formation rate of CaSki and Hela cells decreased and the distribution of G_1 phase decreased, while the distribution of G_2/M phase increased. Inhibition of the expression of endogenous MALAT1 was shown to decrease the expression of cell cycle regulatory molecules (cyclin D1, cyclin E and CDK6), suggesting that the effect of MALAT1 on radiosensitivity may be related to cell cycle regulation, and that the inhibitory effect of miR-145 may also be associated with the regulation of cell cycle regulatory molecules [91]. It was confirmed that MALAT1 and miR-145 had a bidirectional role in RNA-induced silencing complex (RISC), and the downregulation of MALAT1 expression and upregulation of miR-145 expression were more significant in enhancing radiosensitivity than was the upregulation of miR-145 expression alone [90]. It was speculated that the MALAT1-miR-145 axis regulates the radiosensitivity of CC cells infected with high-risk human papillomavirus.

Recent studies also found silencing MALAT1 decreased the viable cell ratio, promoted apoptosis, increased G_1 phase cells, and decreased G_2/M phase cells. Further studies showed that MALAT1 exerted its roles in CC cells via interacting with miR-143. Silencing MALAT1 combined with miR-143 plus radiotherapy decreased the viable cell ratio, enhanced apoptosis, increased G_1 phase ratio, and decreased the numbers of S or G_2/M cells. Therefore, MALAT1 interacts with miR-143 to modulate cell survival, apoptosis, and cell cycle, thus increasing the radiosensitivity of CC [92].

lncRNA growth arrest special 5 (GAS5), a tumor suppressor, is downregulated in many kinds of cancers, including CC. GAS5 is a major participant in regulating the sensitivity of CC cells to radiotherapy, both *in vitro* and *in vivo*. Immediate early response 3 (IER3), also known as IEX-1, is expressed in a wide range of human tissues, including CC tissues. Previous studies have shown that IER expression in CC is significantly reduced, and overexpression of IER3 can promote the apoptosis of CC cells [93]. Schilling et al. [94] found that overexpression of IER3 shortened the cycle of keratinocyte and enhanced its sensitivity to radiotherapy. GAS5 and IER3 are underexpressed in radioresistant SiHa cells, while miR-106b expression is highly expressed. Overexpression of IER3 or GAS5 enhanced radiosensitivity in SiHa cells, while knockdown of IER3 or GAS5 decreased radiosensitivity in ME180 cells. Moreover, GAS5 serves as a miR-106b sponge, and miR-106b negatively regulates IER3 expression. In addition, GAS5 can regulate IER3 expression through miR-106b, and GAS5 enhances radiosensitivity in CC cells through inhibiting miR-106b, both *in vitro* and *in vivo* [95].

It was discovered that NEAT1 was highly expressed in cancer tissues, nonsensitive tissues and radioresistant cancer cells. The overexpression of NEAT1 promoted proliferation, while the silence of NEAT1 made cell cycle arrest in G_0/G_1 phase, and triggered more apoptosis, indicating the oncogenic role of NEAT1 in CC. The mechanistic assays affirmed that NEAT1 could function as a ceRNA to regulate cyclin D1 through sponging miR-193b-3p in CC [96].

Colorectal Cancer

Colorectal cancer (CRC) is one of the most common malignant cancers worldwide, with a 5-year survival rate of about 60% [97]. Radiotherapy is routinely used in CRC treatment to reduce local recurrence and improve the survival rate. However, radioresistance is a major obstacle to radiotherapy, leading to recurrence and poor prognosis. Therefore, understanding the mechanisms of radioresistance and developing novel strategies to increase radiosensitivity are of great importance for the treatment of CRC.

It was found that the expression of lincRNA-p21 was decreased in colorectal cancer cell lines and tissue samples as assessed by expression profile analysis, resulting in increased expression of β-catenin in CRC. The expression of lincRNA-p21 was upregulated and the radiosensitivity of CRC was enhanced by promoting apoptosis when combined with radiation [98]. Wang et al. found that lincRNA-p21 increases the radiosensitivity of CRC cells by promoting apoptosis, and the expression of lincRNA-p21 in SW116 and LOVO cell lines was increased after radiation. After the overexpressing lincRNA-p21 group cells and the control group cells received radiation, it was found that the apoptosis rate of the overexpressing lincRNA-p21 group was higher than that of the control group. The expression of lincRNA-p21 was negatively correlated with that of β-catenin in CRC cells and tissues. Overexpression of lincRNA-p21 significantly inhibited the expression of β-catenin in SW116 cell lines, and the expression of β-catenin was decreased in cell lines after radiation. These results suggest that inhibition of the lincRNA-p21 to Wnt/β-catenin signaling pathway may be involved in the regulation of radiosensitivity of CRC cells. LincRNA-p21 can promote the expression of the apoptosis-promoting gene Noxa. After radiation, the expression level of lincRNA-p21 was increased; thus, the expression of apoptosis-promoting gene Noxa increased. This may provide insight into the molecular mechanism by which lincRNA-p21 increases the radiosensitivity of CRC [99].

lncRNA OIP5-AS1, the lncRNA transcribed in the antisense (AS) direction from the same gene that encodes Opa-interacting protein 5 (OIP5), was initially recognized as cyrano in zebrafish [100]. DYRK1A functions as either an oncogenic factor or a tumor-suppressor in different cancers [101]. Previous research discovered DYRK1A was downregulated by miR-1246 to regulate cell cycle and reduce apoptosis [102]. Zou et al. revealed that OIP5-AS1 binds to miR-369-3p, which further targets DYRK1A, providing a novel insight into the regulatory effect of OIP5-AS1 in CRC. They found OIP5-AS1 and DYRK1A were distinctively downregulated in radioresistant CRC cell lines, implying that OIP5-AS1 and DYRK1A might reduce radioresistance. OIP5-AS1 and DYRK1A decreased cell survival and promoted cell apoptosis after radiation, leading to increase radiosensitivity

of CRC cells. Overexpression of OIP5-AS1 suppressed the expression of miR-369-3p, thus upregulating DYRK1A, the downstream target gene of miR-369-3p, which can reduce viability, induce apoptosis, and enhance radiosensitivity of CRC cells. Thus, OIP5-AS1 can significantly enhance radiosensitivity of CRC cells by regulating DYRK1A through miR-369-3p [103].

UCA1 is highly expressed in CRC cells and downregulation of UCA1 enhances the radiosensitivity of CCL244 cells via inhibition of colony formation, proliferation, and promotion of radiation-induced apoptosis and G_2/M arrest. Moreover, downregulation of UCA1 plus radiation reduced the expression levels of EMT-associated proteins, indicating that silencing of UCA1 significantly inhibits EMT in CCL244 cells [104].

Pancreatic Cancer

Pancreatic cancer (PC) is a highly aggressive potential tumor. More than 80% of pancreatic cancer patients are non-resectable, so radiotherapy, especially concurrent radiotherapy and chemotherapy, is the main treatment for locally advanced pancreatic cancer. Radioresistance is still a challenge for treatment of PC and is one of the main reasons for poor prognosis of PC patients. Pancreatic ductal adenocarcinoma (PDAC) is one of the most common PCs, which has serious radiation resistance. New ways to improve the radiation sensitivity of PC are urgently needed.

HOTAIR has been found to play an oncogenic role in several cancers. The expression of HOTAIR was significantly increased in PDAC cell lines and tissues. After HOTAIR was knocked out, the expression of Wnt inhibitor 1 (WIF1) was increased and the Wnt/β-catenin signaling pathway was inhibited, resulting in decreased expression of the EMT-related protein β-catenin, which increased the radiosensitivity of PDAC cells and increased the cell apoptosis after radiotherapy [105]. Wu et al. found that the expression of HOTAIR was increased in PANC-1 and AsPC-1 cells after radiation. They identified that HOTAIR knockdown could enhance radiosensitivity and influence autophagy by upregulating ATG7 expression in PC cells. In further rescue experiments using rapamycin, activation of autophagy was shown to reverse the inhibition of cell proliferation and colony formation, as well as promoting apoptosis mediated by HOTAIR knockdown, indicating that HOTAIR knockdown increased radiosensitivity of PC cells by regulating autophagy [106].

It is widely accepted that autophagy plays an important protective role in cancer cells during radioresistance [107]. Inhibition of autophagy is vital for the improvement of efficacy of radiotherapy in cancer. When cancer cells are subject to radiation, DNA double-strands are destroyed and proliferative capacity is diminished. The main function of autophagy is to maintain

degradation of the intracellular metabolic balance and to protect cells from radiation-induced cellular damage, as well as to enhance radioresistance, ultimately allowing cancer cells to survive radiation therapy. Studies have demonstrated that suppression of cancer cells autophagy increase the radiation sensitivity of cancer cells [108,109].

LINC00673 plays an anti-oncogene role in PDAC, which can inhibit the proliferation of PC epidermal cells and block the cell cycle in G_0/G_1 phase. LINC00673 interacts with cells and proteins, the most important of which is protein tyrosine phosphatase non-receptor 11 (PTPN11). Overexpression of LINC00673 inhibits activation of the SRC-ERK carcinogenic signaling pathway, inhibits the growth of PDAC cells, and promotes expression of the STAT1 tumor-suppressor signaling pathway. PTPN11 reverses these effects. LINC00673 regulates the ubiquitination of PTPN11 by affecting the binding of PTPN11 to proteins, such as protein PRPF19, which contains ubiquitin ligase and forms a complex with ubiquitin substrates [110]. However, the specific relationship between LINC00673 and radiosensitivity of pancreatic cancer remains unclear.

Gastric Cancer

Gastric cancer (GC) was one of the most common gastrointestinal cancers and is also the second leading cause of cancer-related mortality worldwide. It is difficult to diagnosis GC at an early stage as there are no specific symptoms [111]. Thus, many GC patients are diagnosed at advanced stage, and some postoperative patients with GC should be treated with radiotherapy to reduce the local recurrence rate. Poorly differentiated GC cells are associated with radiation resistance [112]. However, the molecular mechanism underlying radiation resistance is still unknown. Therefore, it is important to identify the molecular mechanism to develop new therapeutic strategies.

Recent studies indicated that lincRNA-p21 plays important roles in the sensitivity of radiotherapy. Chen et al. demonstrated that the expression level of lincRNA-p21 was downregulated in GC tissues and cell lines. Moreover, ectopic expression of lincRNA-p21 suppressed GC cell proliferation, cell cycle, and migration. Furthermore, they found that the radiation increased the expression level of lincRNA-p21 in both the HCG-27 and SGC7901 cells, and elevated expression of lincRNA-p21 increased the radiotherapy sensitivity of GC cells. In addition, they showed that ectopic expression of lincRNA-p21 suppressed β-catenin and c-myc expression. Overexpression of lincRNA-p21 inhibited the GC cell proliferation and increased the radiosensitivity of GC cells by regulating the Wnt/β-catenin signaling pathway, the activation of which is one of the most common features of GC [113].

Linc00673 plays an oncogene role in the genesis and development of GC. The promoter region of linc00673 contains a transcription factor SP1 binding site. Linc00673 can interact with histone methyltransferase (EZH2) and histone demethylase (LSD1) to promote the binding of proteins to promoters of tumor-suppressor Kruppel-like transcription factor 2 (KLF2) and large tumor-suppressor gene 2 (LATS2), thereby inhibiting the expression of tumor-suppressor factors [114].

TINCR plays an oncogene role in the occurrence and development of GC. SP1 can induce the upregulation of TINCR, while TINCR can affect the stability and transcription of KLF2 mRNA. *KLF2* can regulate the transcription and expression of cyclin-dependent kinase genes *p21* and *p15* [115]. However, the lack of p21 protein can weaken radiation-induced cell cycle arrest [116]. It is speculated that TINCR may be associated with radiation resistance, but further studies are needed.

HOTAIR can bind to miR-31-3p and inhibits its function, resulting in the upregulated expression of human epidermal growth factor receptor 2 (HER2) and promoting EMT through the HER2/AKT/HSF-1/Slug signaling pathway [117]. EMT can lead to radiation resistance. Although the mechanism of radiotherapy resistance is known in GC, specific information on its radiosensitivity is still lacking. The interaction between radiotherapy and the above lncRNAs should be explored in depth.

Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC), a principal cause of cancer-related death globally, is associated with a relatively high incidence of 850 000 new cases annually [118]. There have been diverse treatments for HCC, such as surgical resection, liver transplantation, radiotherapy, and chemotherapy [119]. Although surgery is still the main treatment for HCC, radiotherapy will play an increasingly important role in the treatment of HCC with the development of precise radiotherapy. However, the unavoidable radiotherapy resistance has made it difficult to cure HCC by radiotherapy. Therefore, it would be important to elucidate the potential mechanism, which could overcome the radiotherapy-resistance of HCC.

Studies have shown that TUG1 can be used as a biological target for hepatocellular carcinoma to enhance radiosensitivity. Nuclear transcription factor SP1 can induce the overexpression of TUG1, which can bind to comb inhibitory complex 2 (PRC2) and be recruited to the promoter region of KLF 2, thereby inhibiting the transcription of KLF 2 [120]. Loss of the *KLF2* gene leads to decreased neovascularization ability to recruit smooth muscle cells, resulting in decreased neovascularization stability [121–123].

Studies have shown that a combination of radiation therapy and angiogenesis inhibitors can enhance the efficacy of radiation therapy [124]. XIST can inhibit the growth of HCC cells and upregulate PTEN protein, thus delaying the repair of DNA double-strand breaks, blocking the cell cycle in G2/M phase, and increasing radiosensitivity [125]. It was found that miRNA-181a could act on the tumor-suppressor gene *PTEN*. The decrease of PTEN protein prevented phosphoinositol (3,4,5)-triphosphate (PIP3) from dephosphorylating and activated AKT promoted tumor cell growth, invasion, and metastasis by catalyzing phosphorylation of protein, thus leading to radiotherapy resistance [98]. Other studies have shown that XIST can inhibit the above process mediated by miRNA-181a [126].

H19, a paternally imprinted gene located in 11p15.5, has increasingly been found to be overexpressed within various cancers, including HCC [127]. miR-193a-3p is significantly down-regulated in HCC tissues in comparison to the corresponding peri-tumoral tissues, suggesting that this it might be tumor-suppressive for HCC [128]. In addition, presenilin-1 (PSEN1), a primary component of the γ-secretase complex, was demonstrated to be suppressed by miR-193a-3p, and it is probably associated with the radiosensitivity of EC cells [129]. When exposed to radiation, the underexpression of H19 and over-expression of miR-193a-3p tended to significantly elevate the survival rate and proliferation of Bel-7402 cells. H19 was also found to directly target miR-193a-3p in the development of HCC. PSEN1 appears to be subject to the regulation of H19 and miR-193a-3p in its effects on the survival rates and proliferation of HCC cells. The H19/miR-193a-3p/PSEN1 axis can be regarded as containing the treatment targets for HCC, so as to further improve the efficacy of radiotherapies for HCC [130].

Conclusions and Prospects

Recent studies have confirmed that lncRNAs play an important role in the occurrence and development of various malignant tumors. At present, different lncRNAs are known to promote or inhibit the effect of radiation therapy in varying degrees. The role of lncRNAs in radiotherapy of malignant tumors is dual. Partial lncRNAs can enhance radiosensitivity, while other partial lncRNAs can enhance radioresistance. Therefore, the highly expressed lncRNAs can be specifically silenced for radioresistant patients and the related signaling pathways can also be monitored to predict the therapeutic effect and prognosis of cancer patients so as to carry out more effective individualized radiation therapy. At present, the radiotherapy resistance of lncRNAs in EC has been thoroughly researched, and patients with EC who are sensitive to radiotherapy have obvious curative effects and high tolerance. Therefore, the effect of lncRNAs on radiotherapy sensitivity can be regarded as a breakthrough in treatment of patients with radiation resistance to achieve effective radiotherapy.

The study of lncRNAs in radiotherapy is still in the initial stage, and the specific molecular biological mechanisms by which lncRNAs regulate radiosensitivity have not yet been fully described. Clinical trials for evaluating such lncRNAs related to ESCC radiosensitivity are also lacking. Although no promising lncRNAs have been applied in the clinic, we believe more and more specific mechanisms by which lncRNAs regulate radio-sensitivity and radioresistance of malignant tumors will be found with further study of the role of lncRNAs in radiotherapy, which will provide new sensitization strategies for radiotherapy of malignant tumors.

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