Role of autophagy-modulating long non-coding RNAs in tumor radioresistance (Review)

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Abstract. Radiotherapy improves survival rates in patients with cancer; however, the development of radioresistance hinders its effectiveness, resulting in unfavorable outcomes. A key factor in cancer progression is the dysregulation of autophagy, a lysosomal degradation process governed by various evolutionarily conserved autophagy-related genes (ATGs). Long non-coding RNAs (lncRNAs) serve a crucial role in the regulation of autophagy. lncRNAs modulate ATGs and their signaling pathways, contributing to the emergence of radioresistance. The present review offers a comprehensive examination of the critical roles of autophagy and lncRNAs in mediating radioresistance. By enhancing the understanding of these mechanisms, novel therapeutic strategies aimed at increasing tumor radiosensitivity through the modulation of autophagy may be revealed.

Contents

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1. Introduction

Radiotherapy remains a major treatment option for numerous patients, serving both as a radical therapy and as palliative care (1,2). Since the discovery of X-rays by Wilhelm Conrad Röntgen in 1895, the field of radiotherapy has undergone marked evolution (3). This advancement has been driven by the pioneering contributions of renowned scientists such as Nikola Tesla, Mihajlo Idvorski Pupin and Maria Sklodowska-Curie (4). Their innovative efforts have established a solid foundation for modern clinical applications of radiotherapy, which can be employed individually or in combination with other therapies for both curative and palliative purposes at all stages of cancer (5,6). More than half of all patients with cancer undergo radiotherapy; however, its effectiveness is often diminished by the emergence of radioresistance, which can profoundly impact the quality of life of patients (7,8). Radiation therapy exerts its effects by destroying cancer cells either directly or indirectly through the induction of DNA damage. Ionizing radiation (IR) can also activate several prosurvival signaling pathways, including the p53, ataxia telangiectasia mutated and NF-κB pathways, which enhance DNA damage checkpoint activation, promote DNA repair and stimulate autophagy (9-11). Together, these signaling pathways provide protection to cancer cells against radiation-induced damage, thereby contributing to their resistance to treatment (12).

Autophagy is a vital protein degradation pathway in cells, and is essential for maintaining cellular homeostasis and overall health (13). Autophagy, which was first identified in human liver cells, is categorized into three forms in mammalian cells: Macroautophagy, microautophagy and chaperone-mediated autophagy (14). The autophagy process typically includes four main stages: Initiation, formation and maturation of the autophagosome, precise fusion of the autophagosome with the lysosome, and finally content degradation (15) (Fig. 1). During the autophagy process activated by radiotherapy, a cellular mechanism directs old, damaged or malfunctioning biomolecules and organelles to lysosomes for degradation (16,17). This process is preserved through evolution and is triggered by different internal and external stressors, including nutrient shortage, absence of growth factors, IR or low oxygen levels (18). Under such circumstances, autophagy functions primarily as a survival tactic

by clearing out dysfunctional organelles or toxic aggregates that could otherwise lead to apoptosis (19). Furthermore, the lysosomal decomposition of excess cellular parts supplies crucial raw materials and nutrients that can be reused to create important biomolecules (20). Therefore, regulating tumor autophagy levels to reduce radiotherapy resistance represents a novel approach.

Long non-coding RNAs (lncRNAs) are defined as transcripts longer than 200 nucleotides that do not encode proteins (21). Despite their low conservation across species, lncRNAs function as molecular switches that influence cell survival, inflammation and lipid metabolism in the vasculature by regulating autophagy (22). Research has established a relationship between lncRNAs and resistance to tumor radiotherapy (23,24). Additionally, lncRNAs serve various roles, including acting as molecular signals, decoys, guides and scaffolds (25). Therefore, reviewing the role of autophagy-modulating lncRNAs in tumor radioresistance can enhance the understanding of these regulatory mechanisms and may lead to the identification of novel therapeutic strategies aimed at increasing tumor radiosensitivity through the modulation of autophagy.

The present review aims to present the current understanding of the role of autophagy in cancer and its impact on tumor radioresistance through interactions with lncRNAs. By elucidating the function of autophagy-modulating lncRNAs in tumor radioresistance, the present review aims to provide valuable insights into the context-dependent applications of therapeutic strategies.

2. Autophagy in cancer

The role of autophagy in cancer is complex and can be viewed as a double-edged sword; it has the potential to inhibit tumor development, while also being implicated in tumor initiation (26). Autophagy operates at a basal level in all cell types and actively contributes to tumor prevention (27). As a critical intracellular mechanism, autophagy effectively responds to genotoxic stress through pathways involving reactive oxygen species (ROS), helping to prevent the accumulation of mutations and maintain genetic stability (28). Furthermore, autophagy is responsible for the removal of damaged organelles, ensuring that cellular damage does not accumulate, thereby preserving homeostasis and normal cellular function (29). This underscores its precise, standardized and essential role in maintaining cellular health and stability (30).

Among the numerous regulators of autophagy that have been identified, beclin 1 (BECN1) is recognized as one of the most crucial (31). As a vital regulatory protein, BECN1 is essential for initiating autophagy and serves a role in maintaining the delicate balance between cell survival and death (32). Research has indicated that heterozygous loss of the BECN1 gene enhances tumor development in mice, highlighting its importance in understanding the mechanisms underlying tumorigenesis (33). Notably, the deletion of the BECN1 gene is frequently observed in various malignant tumors, including breast, ovarian and prostate cancer, underscoring its critical role in cancer pathology (34-36). Furthermore, a study has demonstrated that overexpression of BECN1 in breast cancer cells effectively inhibited cell proliferation and colony formation, and reduced tumor growth in nude mice (37). In addition to BECN1, research has shown that the knockout of the autophagy-related gene (ATG)5 and ATG7 genes in mice disrupts the autophagy process, leading to exacerbated oxidative stress responses and an increased risk of developing liver cancer (38). These findings emphasize the crucial role of autophagy in tumor prevention.

Autophagy can promote the occurrence and development of tumors (39). Tumor cells can be likened to 'small strongholds' existing in a challenging environment, with autophagy serving as their 'super housekeeper'. This process efficiently recycles large biomolecules, enabling the cells to thrive while also helping to clear cellular damage and prevent serious injuries. Thus, autophagy may function as a 'behind-the-scenes hero' in sustaining and promoting cancer cell proliferation (40). Notably, in some cancer cells, the level of autophagy is higher than that in normal cells, likely as an adaptive mechanism to meet their elevated metabolic demands (41). This suggests that autophagy serves a diverse and intricate role in tumor survival. Additionally, autophagy has been linked to enhanced migration and invasion of cancer cells, particularly in hepatocellular carcinoma (HCC) (42). Furthermore, it serves a role in maintaining the characteristics of cancer stem cells (CSCs) in breast cancer cell lines (43). In general, autophagy serves a crucial role in maintaining genomic integrity, supporting cellular metabolism and ensuring cell survival.

3. Influence of autophagy on the radiation response of tumors

Although radiotherapy is a main approach for the treatment of cancer, resistance frequently arises, resulting in unsuccessful treatments (44). This radioresistance arises from the capacity of tumors to disrupt stress responses, such as DNA damage and repair processes, which either promote or inhibit autophagy and aid in nutrient recycling (45) (Fig. 2). For example, by modulating Unc-51 like autophagy activating kinase 1 (ULK1)-mediated autophagy, butyrophilin subfamily 3 member A1 contributes to tumor progression and radiation resistance in esophageal squamous cell carcinoma (46). Xu *et al* (47) reported that blocking autophagic flux and DNA repair in tumor cells could enhance the effectiveness of radiotherapy for orthotopic glioblastoma. In addition to damaged proteins, various intermediate molecules, their complexes, and organelles such as mitochondria and micronuclei can serve as cargo for the autophagy process (48). Previous studies have revealed both pro-survival and anti-survival characteristics of autophagic pathways (49,50). Cancer cells frequently take advantage of the dual role of autophagy to survive in metabolically difficult conditions, escape immune system attacks, prevent cell death and induce metastasis (51,52). Research has revealed that using both radiation and berberine together suppresses autophagy and alternative end-joining DNA repair, which are linked to radioresistance, thereby enhancing sensitivity to radiation (53).

4. Effect of autophagy on IR-induced cell death

The sensitivity of tumor cells to radiation is frequently affected by autophagic processes (54). BECN1 moves to the nucleus

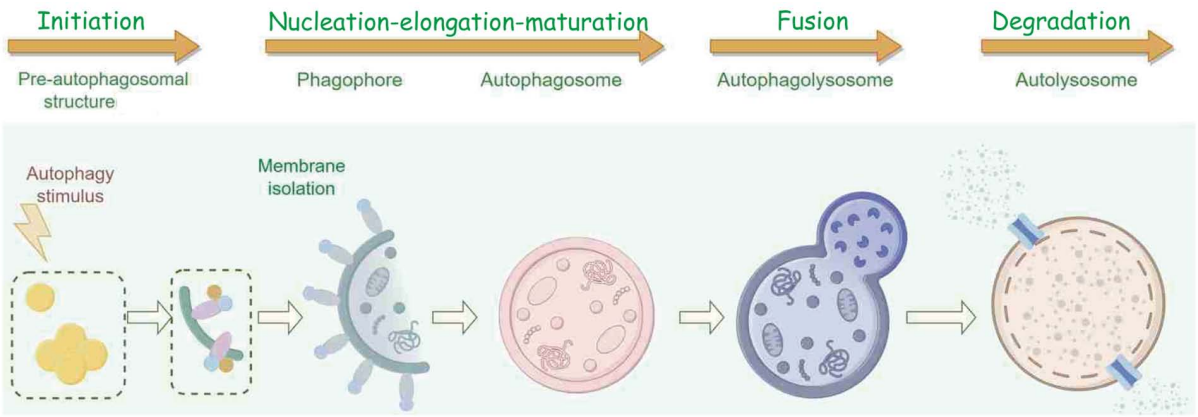

Figure 1. Diagram of the autophagy process. There are four main stages: Initiation, formation and maturation of the autophagosome, precise fusion of the autophagosome with the lysosome, and finally content degradation. This figure was created using Figdraw (version 2.0) (https://www.figdraw.com/).

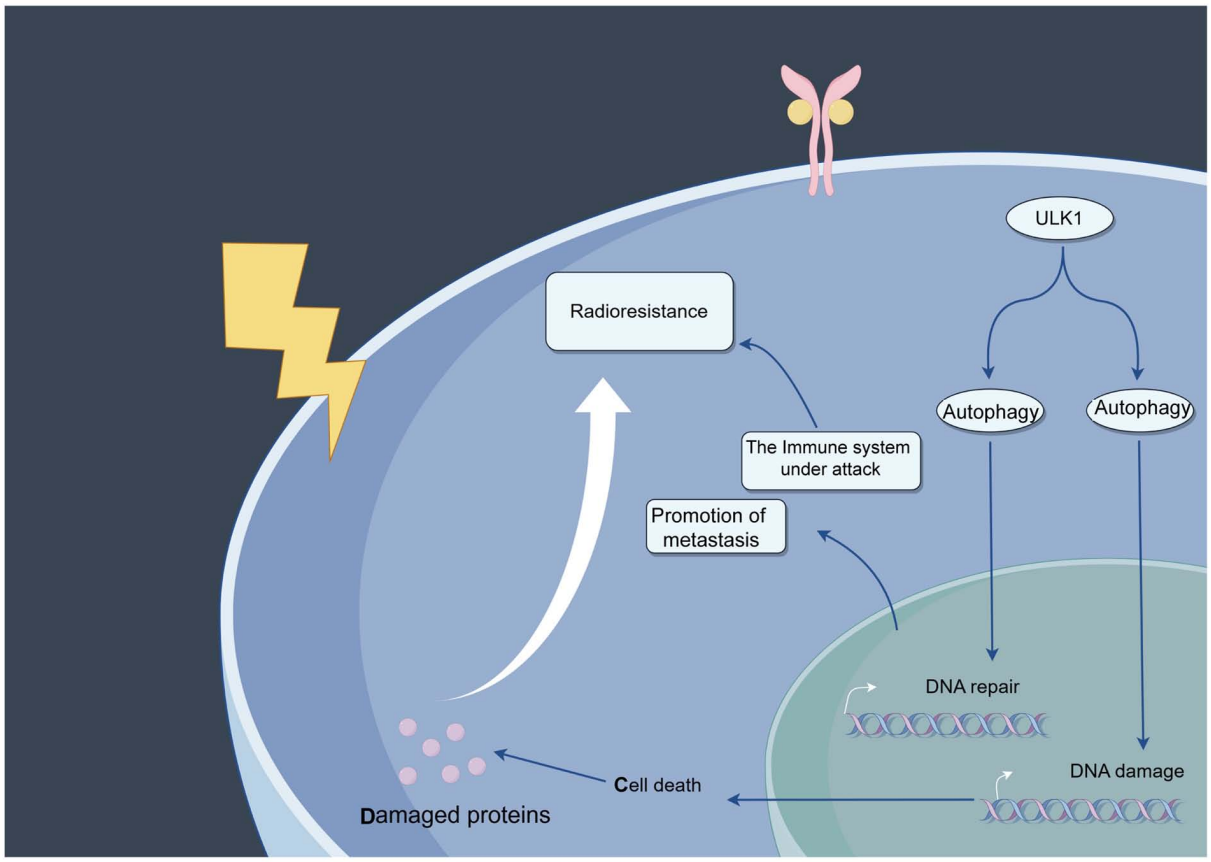

Figure 2. Influence of autophagy on the radiation response of tumors. Autophagy influences the radiation response by modulating DNA damage and repair mechanisms. ULK1, Unc-51 like autophagy activating kinase 1.

after IR exposure, resulting in G_2/M cell cycle arrest (55). Furthermore, autophagy driven by ATG5 has been demonstrated to increase the radiosensitivity of prostate cancer cells, especially when nutrients are scarce or glutamine is depleted, and also when MYC is silenced (56). Chen *et al* (57) proposed that inhibiting the nuclear factor erythroid 2-related factor 2 (NRF2) antioxidative pathway could make U-2 osteosarcoma cells more sensitive to radiation, with the NRF2 antioxidative response being controlled by autophagy-driven activation of ERK 1/2 kinases. Consequently, reducing the expression levels of BECN1, ATG5 or NRF2 has been shown to decrease the IR sensitivity of cancer cells. Furthermore, the inhibition of ATG7 by lncRNA HOTAIR, which is notably upregulated in prostate cancer cell lines exposed to radiation, has been associated with radioresistance in these cells (58). These results emphasize the essential function of autophagy in influencing radiosensitivity and suggest the possibility of targeting autophagic pathways to enhance radiotherapy effectiveness (58).

Research on breast cancer cells, which naturally resist apoptosis, further underscores the link between IR and autophagic pathways (59). After IR exposure, these cells show increased autophagic characteristics, resulting in more iron

accumulation. This accumulation, in conjunction with subsequent ROS generation, oxidative stress and DNA damage, may trigger cell death through a mechanism known as ferroptosis (60,61). These insights have sparked a rising interest in pairing autophagic inducers with IR to improve the radiosensitivity of cancer cells. For instance, in a similar approach, the treatment of non-small cell lung carcinoma (NSCLC) cells with rapamycin alongside a histone deacetylase inhibitor has been found to promote radiosensitization (62). This combined treatment has two effects: It boosts autophagy and at the same time hinders DNA damage repair processes. Observations in cultured cells and tumor xenograft mouse models have demonstrated the effectiveness of the strategy, pointing to a potential improvement in radiotherapy outcomes (63).

Autophagy affects cancer cell survival in complex ways, acting both as a supporter and an opponent of radiosensitization (62,64). Various cancer cell types have been shown to exploit enhanced autophagy as a survival strategy. For instance, the application of autophagy inhibitors renders otherwise radio-resistant bladder cancer (BLCA) cells more sensitive to chemotherapy (65). Similarly, silencing of ATG5, a key component of the autophagy process, has been found to increase IR-induced cell death in nasopharyngeal carcinoma (66). Furthermore, the use of autophagy inhibitors in combination with IR has emerged as a factor influencing the bystander and abscopal effects associated with chemotherapy and radiotherapy (67). These findings underscore the importance of context in the role of autophagy in cancer treatment and highlight the potential of targeting autophagy pathways to enhance treatment efficacy.

5. Effect of autophagy on CSCs and the IR response

Autophagy serves a vital role in preserving the stemness of CSCs (68). A number of tumors activate the epithelial-mesenchymal transition (EMT) program to acquire stem cell-like properties, facilitating their growth, invasion and metastasis (69). A study involving cervical cancer cells has shown that ATGs, especially ATG5, are crucial in the EMT process (70). Autophagy is crucial for enhancing tumor growth, invasiveness and maintaining stem cell-like traits in radio-resistant cancer cells, including pancreatic ductal adenocarcinoma and NSCLC stem cells (71,72). As a result, autophagy inhibitors, either on their own or alongside conventional cancer treatments, have been successful in preventing cell proliferation, colony formation and spheroid formation in pancreatic CSC populations (73). Additionally, the suppression of crucial autophagic genes, including Atg5, has been identified to enhance radiosensitivity in radio-resistant CSCs, such as those found in prostate cancer (56). These results emphasize the complex function of autophagy in maintaining CSC characteristics and its potential as a therapeutic target to improve treatment results.

6. Effect of IR on tumor autophagy

Radiotherapy is a common cancer treatment that induces different forms of cell death, including autophagy (74). Besides directly causing DNA strand breaks, IR can lead to the production of significant amounts of ROS in cells, resulting in oxidative stress damage (75). According to Yang *et al* (76), mitophagy triggered by IR boosts ferroptosis by raising the levels of free fatty acids inside cells. Lysosomes serve a crucial role in autophagy, a cellular degradation process (77). A conserved protein associated with autophagy, Atgs/P62/LC3II, controls the process (78). In cancer cells, autophagy is a double-edged sword. In the initial phases, it might restrict the development of tumors. Nevertheless, it might also offer a survival advantage for adaptation and detoxification in challenging conditions such as starvation, low oxygen levels, and chemotherapy or radiotherapy (79). Investigators have reported that autophagy activity rises following IR. This acts as a mechanism for cells to survive when faced with cytotoxic agents, including IR and temozolomide, in the treatment of glioblastoma (80,81). Furthermore, researchers have revealed that IR promotes autophagy via the Wnt/β-Catenin pathway (82). In conclusion, IR has an important effect on tumor autophagy.

7. lncRNA-mediated autophagy in cancer

Numerous cancer types have been found to exhibit abnormal expression of lncRNAs, and the relationship between lncRNAs and autophagy has garnered interest across various cancer types (Table I), including lung, gastric, breast and prostate cancer (83). The majority of research suggests that lncRNAs regulate autophagy mainly through mechanisms such as microRNA (miRNA/miR) sponging (functioning as competing endogenous RNAs), interactions between RNAs, RNA-protein regulation and various other pathways (84,85). Studies have indicated that lncRNAs are involved in various phases of the autophagy process from the beginning to the maturation stage (86,87). They assist in starting autophagic phagocytosis by controlling essential proteins such as ULK1, mTOR and BECN1, and they also affect the extension of autophagic vesicles by regulating ATG3, ATG5, ATG4, ATG12 and ATG7 (88). The present review highlights the complex and diverse functions of lncRNAs in regulating autophagy, and their possible impact on cancer biology and treatment.

Proliferation is one of the most critical malignant phenotypes observed in cancer, while apoptosis is equally significant in the context of neoplastic development (89). Although their functions are fundamentally opposite (proliferation promotes cell growth and survival, while apoptosis leads to programmed cell death), their interactions work synergistically to regulate cancer development. This delicate balance between cell proliferation and apoptosis serves a crucial role in tumor progression and resistance to therapy (90). In digestive system cancers, various lncRNAs have been identified to serve roles in tumor progression and autophagy regulation (91). For instance, lncRNA SNHG11 is upregulated in gastric cancer and is associated with poor patient prognosis. lncRNA SNHG11 post-transcriptionally enhances ATG12 expression through miR-1276, thereby promoting autophagy, cell proliferation and activation of the Wnt/β-catenin signaling pathway (92). Similarly, in HCC, lncRNA MALAT1 exhibits elevated expression levels compared with those in normal tissues. Silencing MALAT1 has been shown to increase HCC autophagy by promoting the conversion of LC3-I to LC3-II and simultaneously suppressing HCC cell proliferation (93). Conversely, lncRNA NBR2 acts as a tumor suppressor in HCC by inhibiting BECN1 and autophagy through the ERK/JNK

Table I. lncRNA-mediated autophagy in various cancer types.

First author/s, year	lncRNAs regulating autophagy	Regulatory mechanism	Tumor type	(Refs.)
Wu *et al*, 2021	lncRNA SNHG11	ATG12	Gastric cancer	(92)
Chen *et al*, 2020	lncRNA MALAT1	LC3-I/II	Hepatocellular carcinoma	(93)
Sheng *et al*, 2021	lncRNA NBR2	BECN1	Hepatocellular carcinoma	(94)
Wang and Jin, 2019	lncRNA SLCO4A1-AS1	miR-508-3p/PARD3	Colorectal cancer	(95)
Wang *et al*, 2022	FIRRE	BECN1	Colorectal cancer	(96)
Lu *et al*, 2021	LINC01207	miR-1301-3p/LDHA	Oral squamous cell carcinoma	(97)
Jiang *et al*, 2021	LINC00958	BECN1 and ATG5	Oral squamous cell carcinoma	(98)
Lu *et al*, 2020	lncRNA HOTAIR	miR-204-5p/HMGB1	Cholangiocarcinoma	(99)
Wu *et al*, 2023	LZTS1-AS1	miR-532/TWIST1	Pancreatic cancer	(101)
Lv *et al*, 2020	lncRNA TUG1	miR-31-5p/FLOT1	Clear cell renal cell carcinoma	(102)
Zhang *et al*, 2020	lncRNA ADAMTS9-AS2	PI3K/AKT/mTOR	Bladder cancer	(104)
Li *et al*, 2018	lncRNA CASC2	miR-214/TRIM16	Non-small cell lung cancer	(105)
Peng *et al*, 2021	lncRNA SLC26A4-AS1	ETS1	Papillary thyroid carcinoma	(106)
Qin *et al*, 2022	lncRNA SNHG5	RBM47/SNHG5/FOXO3	Papillary thyroid carcinoma	(107)

ATG, autophagy-related gene; BECN1, beclin 1; FLOT1, flotillin 1; HMGB1, high mobility group box 1; LDHA, lactate dehydrogenase A; lncRNA, long non-coding RNA; miR, microRNA; PARD3, par-3 family cell polarity regulator; RBM47, RNA binding motif protein 47; SNHG5, small nucleolar RNA host gene 5; TRIM16, tripartite motif containing 16; TWIST1, twist family bHLH transcription factor 1.

pathways, thereby restraining HCC cell proliferation (94). In colorectal cancer (CRC), lncRNA SLCO4A1-AS1 acts as an oncogenic element, exhibiting a positive association with par-3 family cell polarity regulator (PARD3) and sponging miR-508-3p. This lncRNA enhances the proliferation of CRC cells and initiates autophagy through the miR-508-3p/PARD3 pathway. Nonetheless, the regulatory effect is interrupted by the application of the autophagy inhibitor 3-methyladenine (95). Another lncRNA in CRC, FIRRE, directly interacts with polypyrimidine tract binding protein 1 to enhance BECN1 mRNA stability, thus reducing autophagy and promoting CRC cell proliferation (96). In the context of oral squamous cell carcinoma (OSCC) and cholangiocarcinoma (CCA), several upregulated lncRNAs have been shown to suppress autophagy. For instance, LINC01207 is highly expressed in OSCC, where its upregulation promotes cell proliferation but inhibits both apoptosis and autophagy via the miR-1301-3p/lactate dehydrogenase A axis (97). By contrast, overexpression of LINC00958 reduces apoptosis while promoting autophagy by upregulating autophagy-related proteins such as BECN1 and ATG5, and increasing the LC3-II/LC3-I ratio, driven by p53 mediated by sirtuin 1 (SIRT1) (98). In CCA, lncRNA HOTAIR inhibits both apoptotic and autophagic processes, thereby promoting the proliferation of CCA cells by targeting the miR-204-5p/high mobility group box 1 axis (99). Pancreatic cancer (PANC), known for its poor prognosis, remains a complex malignancy with unclear progression mechanisms (100). A study by Wu *et al* (101) revealed that LZTS1-AS1, a highly expressed lncRNA in PANC cells and tissues, promoted PANC cell proliferation while inhibiting apoptosis and autophagy via the miR-532/twist family bHLH transcription factor 1 axis. Overall, these findings highlight the diverse and critical roles of lncRNAs in modulating autophagy and influencing the malignant phenotypes of various cancer types.

Lv *et al* (102) found that silencing TUG1 suppressed cell proliferation while promoting apoptosis and autophagy in ccRCC cells. This effect is considered to be mediated via the miR-31-5p/flotillin 1 axis (102). In addition, lncRNA SCAMP1 has been observed to be upregulated in renal cell carcinoma (RCC) cells and tumors, where it regulates zinc finger E-box binding homeobox 1 and JUN as well as autophagy. This regulation is considered to contribute to oxidative stress-induced RCC in pediatric patients via miR-429 (103). In the context of BLCA, the lncRNA autophagy network serves a crucial role in disease progression. Zhang *et al* (104) demonstrated that ADAMTS9-AS2 inhibited proliferation and enhanced both autophagy and apoptosis through the PI3K/AKT/mTOR signaling pathway.

The downregulation of lncRNA CASC2 enhances apoptosis in NSCLC and diminishes ATG5-mediated autophagy by regulating the miR-214/tripartite motif containing 16 axis in A549 and H1299 NSCLC cell lines (105). Conversely, a reversed autophagic state has been noted in papillary thyroid carcinoma (PTC), where overexpression of lncRNA SLC26A4-AS1 inhibited the proliferation of PTC cells and stimulated autophagy by recruiting the transcription factor ETS1 and elevating inositol 1,4,5-trisphosphate receptor type 1 expression (106). Additionally, Qin *et al* (107) revealed that lncRNA SNHG5 was stabilized by RNA binding motif protein 47 (RBM47) and directed to FOXO3, resulting in decreased proliferation and the activation of autophagy in PTC cells through the RBM47/small nucleolar RNA host gene 5/FOXO3 pathway.

8. Autophagy-modulating lncRNAs and tumor radioresistance

Current studies (108,109) have highlighted the role of several lncRNAs, which primarily regulate autophagy, as significant

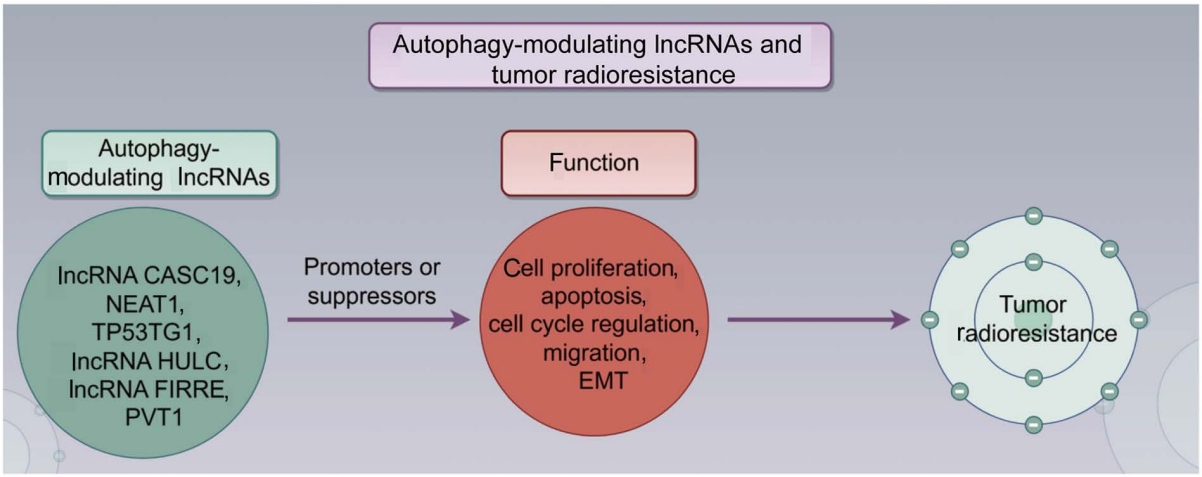

Figure 3. Autophagy-modulating lncRNAs and tumor radioresistance. A number of autophagy-modulating lncRNAs influence tumor resistance to radiotherapy by promoting cell proliferation, apoptosis, metastasis and other related factors. EMT, epithelial-mesenchymal transition; lncRNA, long non-coding RNA.

contributors to tumor radioresistance (Fig. 3), and these lncRNAs are discussed subsequently.

lncRNA CASC19. CASC19, a newly identified lncRNA located on chromosome 8q24.21, consists of 324 nucleotides (110). A study has demonstrated that CASC19 expression is upregulated in a variety of human cancer types, including NSCLC, gastric cancer, CRC, PANC, ccRCC, glioma, cervical cancer and nasopharyngeal carcinoma (111). Notably, some research has indicated that CASC19 can enhance radioresistance in nasopharyngeal carcinoma by modulating autophagy signaling pathways (112,113). Furthermore, the dysregulation of CASC19 has been closely linked to numerous clinicopathological characteristics (prognosis and pathological staging) and cancer progression, particularly in HCC and gastric cancer (114,115). In summary, CASC19 influences various cellular phenotypes, including cell proliferation, apoptosis, cell cycle regulation, migration, invasion, EMT, autophagy and therapeutic resistance (116).

NEAT1. NEAT1 is predominantly located in the nucleus, although a smaller fraction is present in the cytoplasm (117). NEAT1 functions as a structural component of nuclear paraspeckles and is involved in regulating gene expression at both transcriptional and post-transcriptional levels (118). Research has demonstrated that NEAT1 contributes to radioresistance in HCC cells by inducing autophagy through GABA type A receptor-associated protein (119). The role of NEAT1 in carcinogenesis is multifaceted, encompassing interactions with miRNAs, modulation of gene expression, regulation of epigenetic factors and participation in various signaling pathways, such as the PI3K-AKT and TGF-β1 pathways (120). Additionally, the involvement of NEAT1 in cancer is complicated by its impact on CSCs and the tumor microenvironment (121). The interaction of NEAT1 with autophagy further adds to the complexity of its functions in cancer biology (122). Understanding the interactions between NEAT1, autophagy and radioresistance is crucial for researchers as it may lead to the identification of novel therapeutic targets and strategies aimed at disrupting oncogenic processes, reducing treatment resistance and improving patient survival (123). Consequently, this understanding could facilitate the development of specialized treatment approaches and regimens.

TP53TG1. lncRNA TP53TG1 (National Center for Biotechnology Information reference sequence, NR_015381.1), located on chromosome 12, is transcribed as an ~0.7-kilobase lncRNA molecule (124). Its expression can be induced under conditions of cellular stress in a wild-type TP53-dependent manner (125). As a relatively recent discovery in the field of lncRNAs, TP53TG1 has been implicated to serve oncogenic and anti-oncogenic roles across various cancer types, such as gastric and breast cancer (126). For example, overexpression of TP53TG1 promotes proliferation of colon cancer cells (127). In addition, Cheng *et al* (128) found that lncRNA TP53TG1 exerted anticancer effects in cervical cancer by comprehensively regulating the transcriptome profile of HeLa cells. Research has indicated a close association between TP53TG1 and autophagy (129). Furthermore, it has been demonstrated that lncRNA TP53TG1 contributes to the radioresistance of glioma cells through the miR-524-5p/RAB5A axis (130). Given these findings, TP53TG1 represents a promising target to enhance the sensitivity of tumors to radiotherapy.

lncRNA HULC. HULC, found on chromosome 6p24.3, has been identified to be upregulated in HCC and is linked to cancer advancement (131). The expression of this transcript is regulated by miRNAs and transcriptionally modulated by Sp1 family factors (132). HULC has been identified as a novel biomarker in different types of cancer, such as prostate cancer and CRC, serving a role as an oncogenic factor (133). Research conducted previously indicated that inhibiting HULC could reduce angiogenesis in human gliomas (134). Another study demonstrated that HULC facilitated the advancement of CRC (135). A study has shown that lncRNA HULC serves a role in radioresistance by reducing autophagy in prostate cancer cells (136). Thus, lncRNA HULC could serve as a therapeutic target to combat tumor resistance to radiotherapy.

lncRNA FIRRE. FIRRE is a lncRNA that is conserved and found on the X chromosome (137). FIRRE is associated with reduced overall survival in neuroblastoma and has been found to promote cell proliferation in lymphoma (138). According to Shi *et al* (139), lncRNA FIRRE is triggered by MYC and facilitates the progression of diffuse large B-cell lymphoma through the Wnt/β-catenin signaling pathway. FIRRE is a lncRNA associated with autophagy and serves as a prognostic biomarker for esophageal cancer, which was identified using a bioinformatics approach (140). Cai *et al* (141) revealed that lncRNA FIRRE influenced the sensitivity of endometrial cancer to radiotherapy through autophagy mediated by the miR-199b-5p/SIRT1/BECN1 axis.

PVT1. PVT1, a lncRNA, was initially identified as a driver of variant translocations in mouse plasmacytomas (142). The human lncPVT1 gene is situated on chromosome 8q24.21, sharing the same location as the MYC oncogene (143). lncPVT1 has been identified as a factor that accelerates the development of several cancer types, such as nasopharyngeal cancer and lung cancer (144,145). Radioresistance poses a major challenge to tumor treatment success, and is connected to the abnormal regulation of physiological functions in cancer cells, including apoptosis, autophagy, stemness (for CSCs), hypoxia, EMT and DNA damage repair (146,147). Recently, lncPVT1 has been linked to the modulation of radioresistance in certain cancer types, including nasopharyngeal cancer and lung cancer (148).

9. Challenges and future directions

Research interest in lncRNA therapeutics has only emerged in the past decade, and so far, no treatments targeting lncRNAs have reached clinical development (149). SP100-AS1, a lncRNA that targets the antisense sequence of the SP100 gene, is upregulated in the tissues of patients with CRC who are resistant to radiation, according to RNA-sequencing analysis (150). Notably, reducing SP100-AS1 expression lowered radioresistance and decreased cell proliferation and tumor growth in both laboratory and live models. To identify the proteins and miRNAs interacting with SP100-AS1, mass spectrometry and bioinformatics analyses were utilized. SP100-AS1 was shown to interact with and stabilize the ATG3 protein via the ubiquitination-dependent proteasome mechanism (150). This interaction highlights the possible involvement of SP100-AS1 in regulating autophagy-related mechanisms and enhancing radioresistance in CRC. SP100-AS1 holds potential as a therapeutic target to enhance the response of CRC to radiation therapy (150). As aforementioned, autophagy affects tumor cell proliferation, survival and the response to treatment in intricate ways across different types of cancer, such as nasopharyngeal cancer and CRC. Methods to target autophagy might involve aiming at specific proteins or pathways associated with autophagy, as well as using agents that promote or block autophagy.

Scientists seek to improve treatment effectiveness by utilizing the interaction between autophagy and processes regulated by lncRNAs. They aim to develop more effective treatments by integrating autophagy modulation with lncRNA-targeted methods (151). Furthermore, these combination therapies provide a comprehensive strategy to boost patient outcomes (152).

There are both obstacles and prospects in the future research of radiation oncology and lncRNAomics (153). For precise tumor targeting, technological advancements such as hybrid MRI and positron emission tomography scans are vital, although they entail significant costs and demand specialized expertise (154). One major obstacle in lncRNA research is the restricted knowledge gained from examining just a small portion of lncRNAs, which limits the understanding of their mechanisms, roles and structures (155). Despite significant progress in the field, delivering oligonucleotides to solid tumors continues to be a major challenge. Advancements in artificial intelligence and sophisticated statistical modeling have enabled molecular-guided treatment plans customized for each patient, representing a significant achievement in precision medicine. Autophagy-modulating lncRNAs represent a vast yet largely unexplored reservoir of oncogenes, tumor suppressors and radioresponse modifiers. Integrating this knowledge into treatment strategies, from diagnosis and response prediction to the design of targeted therapies, could greatly enhance management and outcomes for patients with cancer (156). In conclusion, the present review summarizes the effects of autophagy-modulating lncRNAs on tumor radioresistance, providing novel ideas for tumor radiosensitization.

10. Conclusions

lncRNAs that modulate autophagy are crucial elements in the radioresistance of tumors. These lncRNAs are crucial in different stages of cancer development and advancement, such as tumor expansion, spread and resistance to treatment. Studies are concentrating on using autophagy-based treatment methods to tackle radioresistance in patients with cancer (157,158). Modifying autophagy can influence the survival of tumor cells, their response to therapy and the overall success of treatment. Creating targeted cancer treatments requires a deep comprehension of the interaction between lncRNAs and autophagy. Targeting specific lncRNAs could potentially adjust autophagy and increase tumor radiosensitivity. Current clinical trials and preclinical research are investigating the potential of targeting autophagy and lncRNAs to enhance treatment outcomes for patients with cancers resistant to radiation (159,160).

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HL wrote and reviewed the drafts of the paper, while ZH created the figures and tables, and revised the paper. Data authentication is not applicable. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

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Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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