Advances in the role of long non-coding RNAs and RNA-binding proteins in regulating DNA damage repair in cancer cells

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Received June 16, 2023; Accepted August 9, 2023

DOI: 10.3892/ijmm.2023.5296

Abstract. DNA damage and repair play a crucial role in the development, progression and treatment of cancer. In response to various types of DNA damage, the organism initiates a series of DNA damage responses that trigger post-DNA damage repair processes. Among the most severe forms of DNA damage are DNA double-strand breaks (DSBs), which can be repaired by the body through two pathways: Homologous recombination and non-homologous end joining. The repair of DNA damage, particularly DNA DSBs, significantly influences the sensitivity and resistance of cancer cells to chemotherapy and radiotherapy. Numerous studies have demonstrated that long non-coding RNAs (lncRNAs) can exert multiple regulatory effects on cancer cells by binding to RNA binding proteins (RBPs), thereby influencing DNA damage repair. Based on a comprehensive literature search, the existing research on the regulation of DNA damage repair by lncRNAs interacting with RBPs has primarily focused on the repair of DNA DSBs. Therefore, the present review discusses the regulatory effects of the interaction between lncRNAs and RBPs on DNA damage repair in cancer cells, with a specific focus on the repair of DNA DSBs and its implications in cancer. It is hoped that comprehensive analysis may enhance the current understanding of the molecular mechanisms underlying DNA damage repair in cancer and may lead to the identification of novel diagnostic biomarkers and potential therapeutic targets.

Contents

1. Introduction

Various types of DNA damage can occur when cells are exposed to endogenous or exogenous factors, including alterations in base pairs, errors during DNA replication, and twisting and breaking of the DNA double helix strand (1,2). Exogenous factors, such as toxic heavy metals and ionizing radiation are known to cause severe DNA damage (3-7). Endogenous factors are often released during the metabolism of exogenous substances in the body or as a result of cell damage and the loss of cell membrane integrity (8). It is estimated that cells experience ~70,000 DNA lesions per day (9). While the majority of these lesions are single-strand breaks, there are also a few instances of DNA double-strand breaks (DSBs). To cope with this continuously occurring damage, eukaryotic cells have developed a complex and efficient DNA damage response (DDR) system that consists of numerous DNA damage repair pathways (10-12). The primary molecular pathways for DSB repair are homologous recombination (HR) and non-homologous end joining (NHEJ). DSBs are particularly harmful and pose a serious threat to cells. If DSBs are not effectively repaired or undergo error-prone repair, they can lead to carcinogenesis or cell death (13). DNA damage also serves as the foundation of cancer therapy. Chemotherapy and radiotherapy, which are based on inducing severe DNA damage to and the apoptosis of cancer cells, are the preferred treatment regimens

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Abbreviations: DSB, double-strand break; DDR, DNA damage response; HR, homologous recombination; NHEJ, non-homologous end joining; lncRNA, long non-coding RNA; RBP, RNA binding protein; ATM, ataxia telangiectasia mutated; ATR, ATM-and Rad3-related; DNA-PKcs, DNA-dependent protein kinase catalytic subunits; RPA, replication protein A; MRE11, meiotic recombination 11 homolog 1; NBS1, Nijmegen breakage syndrome 1 protein; RAP80, receptor-associated protein 80; ALT-EJ, alternative end joining; HIF-1α, hypoxia inducible factor-1α; EGFR, epidermal growth factor receptor; MCM5, minichromosome maintenance deficient 5; ZCCHC4, zinc finger CCHC domain-containing protein 4

Key words: long non-coding RNA, RNA-binding protein, DNA damage, DNA repair, DNA damage repair, DNA double-strand break, cancer

for the majority of malignancies (14). However, the activation of DNA damage repair pathways can promote resistance to genotoxic drugs, which remains a significant obstacle in the successful treatment of cancer (15,16). Therefore, it is crucial to elucidate the molecular mechanisms underlying DNA damage repair in order to improve the effectiveness of DNA damage-based anticancer therapies.

Long non-coding RNAs (lncRNAs) are a class of RNAs that exceed 200 nucleotides in length and lack protein-coding potential (17). They have garnered significant attention in recent years. There is mounting evidence to suggest that numerous lncRNAs are dysregulated in various types of cancer and play crucial roles in cancer development and progression (18). The involvement of lncRNAs in drug resistance has also been extensively reported (19,20). Through their interactions with RNA, DNA, or proteins, lncRNAs have emerged as potent regulators of numerous cellular processes (21). RNA-binding proteins (RBPs), a group of proteins, are known to directly bind to single- or double-stranded lncRNAs, participating in lncRNA-mediated regulatory activities (22). Furthermore, the function of certain lncRNAs is dependent on their interactions with specific proteins (23). The interplay between lncRNAs and RBPs plays a critical role in regulating cancer development, progression and drug resistance by influencing DNA damage repair. However, the underlying mechanisms involved in this interplay remain poorly understood, thus necessitating further investigations.

The present review provides a comprehensive summary of the mechanisms through which lncRNAs regulate DDR, DNA DSB repair and influence the sensitivity and resistance to chemotherapy and radiotherapy in DNA damage/repair processes in cancer cells by binding to RBPs. The aim of the present review was to elucidate the regulatory mechanisms of lncRNAs and RBPs associated with cancer development, progression and treatment, thereby aiding the development of novel strategies for cancer therapy. A systematic literature search was conducted using PubMed, employing keywords such as 'long non-coding RNA', 'RNA-binding protein', 'DNA damage', 'DNA repair', 'DNA damage repair', 'DNA double-strand break' and 'cancer'. Articles discussing the regulation of DNA damage repair in cancer by lncRNAs through interactions with RBPs were screened and analyzed.

2. lncRNA binding to RBPs regulates the DNA damage response in cancer cells

Genomic DNA in organisms is highly susceptible to both exogenous and endogenous damage. To maintain genomic integrity and prevent genetic instability, cells and organisms rely on mechanisms to preserve the integrity of their genomic DNA (14,15,24). One crucial mechanism is the DDR, a series of rapid cellular processes that are activated upon the detection of DNA damage (25). The DDR pathway comprises sensors, receptors and effectors that sense DNA damage, propagate signals and initiate appropriate responses, including cell cycle arrest, DNA repair or apoptosis (26-28). In addition to its role in precise cell replication and genome maintenance, there is increasing evidence to indicate that he DDR is involved in resistance to DNA damage-based chemotherapy and radiotherapy (29). It has been observed that molecules expressed as proteins in the DDR pathway can modulate the effects of chemotherapy and radiotherapy (30). Following DNA damage, the ataxia telangiectasia mutated (ATM) kinase is activated through autophosphorylation at the site of damage. ATM, in turn, phosphorylates downstream substrates, including the tumor suppressor p53, breast cancer type 1 susceptibility protein (BRCA1) and checkpoint kinase (CHK)2. These effector molecules transmit DNA damage signals and activate cell cycle checkpoints, DNA repair and apoptosis (24,31,32). Research has highlighted the significant regulatory role of lncRNAs in the DDR, with a number of proteins binding to lncRNAs and participating in their regulatory activities (22). Therefore, the present review provides a comprehensive summary of the role of lncRNA binding to RBPs in these DDR processes (Fig. 1 and Table I).

Cell cycle checkpoints. DDR involves a series of networks linking tumor suppressor genes to DNA repair pathways, damage tolerance processes, cell cycle checkpoints and apoptosis (24,33). The ATM kinase plays a crucial role as a sensor in the DDR pathway, particularly in detecting DNA DSBs. The ATM-mediated phosphorylation of downstream target proteins initiates signaling cascades that activate cell cycle checkpoints and DNA repair mechanisms (34).

lncRNAs have the ability to directly or indirectly regulate the activation or repression of cell cycle checkpoints through their interactions with RBPs, thereby influencing the DDR. Wan *et al* (35) discovered that lncRNA ANRIL was induced by the E2F1 transcription factor in an ATM-dependent manner following DNA damage. ANRIL interacted with polycomb repressor complex (PRC)1 and PRC2 to suppress the expression of INK4B-ARF-INK4A motifs, specifically p15(INK4b), p16(INK4a) and p14(ARF). This inhibitory effect on gene expression led to the suppression of cell cycle checkpoint activation, promoting cell proliferation and maintaining the DDR (35). In another study, Wan *et al* (36) found that lncRNA JADE inhibited the DNA damage checkpoint and enhanced cell proliferation. Similarly, lncRNA JADE expression was induced in an ATM-dependent manner following DNA damage. JADE acted in collaboration with BRCA1 to mediate the transcriptional induction of JADE1 following DNA damage, resulting in the upregulation of JADE1 expression and increased histone H4 acetylation. These molecular events disrupted the DNA damage checkpoint regulation, impaired the DDR and promoted cancer progression (36). Telomeric repeat sequence-containing RNA (TERRA) is a large non-coding RNA localized in mammalian cells and is a component of telomeric heterochromatin (37,38). The inhibition of telomeric-repeat binding factor 2 (TRF2), a protein involved in telomere maintenance, triggers an ATM-dependent DDR pathway and activates cell cycle checkpoints (39,40). Zhang *et al* (41) demonstrated that TERRA can form a complex with the G-tetraspanin quinoline derivative, CK1-14, which binds to the TERRA G-quadruplex. This complex disrupts the binding of TRF2 to telomeric double-stranded DNA, leading to the induction of a DDR in U2OS cells. Consequently, the cell cycle checkpoint is activated, resulting in cell cycle arrest, the inhibition of cell proliferation and apoptosis. CK1-14 exhibits potential as a lead compound for further development as a novel target for cancer therapy (41).

Table I. lncRNAs bind to RBPs to regulate DNA damage response.

RBP	Mechanism	Role	(Refs.)
PRC1 and PRC2	Inhibition of p15, p16 and p14 expression	Inhibits cell cycle checkpoint activation	(35)
BCRA1	Induced upregulation of JADE1 expression and increased histone H4 acetylation level	Inhibits cell cycle checkpoint activation	(36)
TRF2	Interference with the binding of TRF2 to telomeric double-stranded DNA	Activation of cell cycle checkpoints	(41)
hnRNP I	Inhibition of p53 translation	Inhibition of p53-mediated cell cycle arrest and apoptosis	(42)
PTBP3	Inhibition of p53 activation	Inhibition of p53-mediated cell cycle arrest and apoptosis	(47)
PCBP2	Inhibition of nuclear translocation of p53	Inhibition of p53-mediated cell cycle arrest and apoptosis	(48)
Sam68	Transcriptional co-activator of p53 that enhances p53-mediated cellular responses	Promotes p53-mediated cell cycle arrest and apoptosis	(49)
hnRNPK	Repression of down-regulated genes as part of the typical p53 transcriptional response	Promotes apoptosis	(51)
NF-YA	Block or reject the binding of NF-YA to chromatin and inhibit the expression of pro-apoptotic genes	Inhibition of apoptosis	(52)

lncRNAs, long non-coding RNAs; RBP, RNA binding protein; BRCA1, breast cancer type 1 susceptibility protein; TRF2, telomeric-repeat binding factor 2; PTBP3, polypyrimidine tract binding protein 3; PCBP2, poly (rC) binding protein 2; NF-YA, nuclear transcription factor Y, alpha.

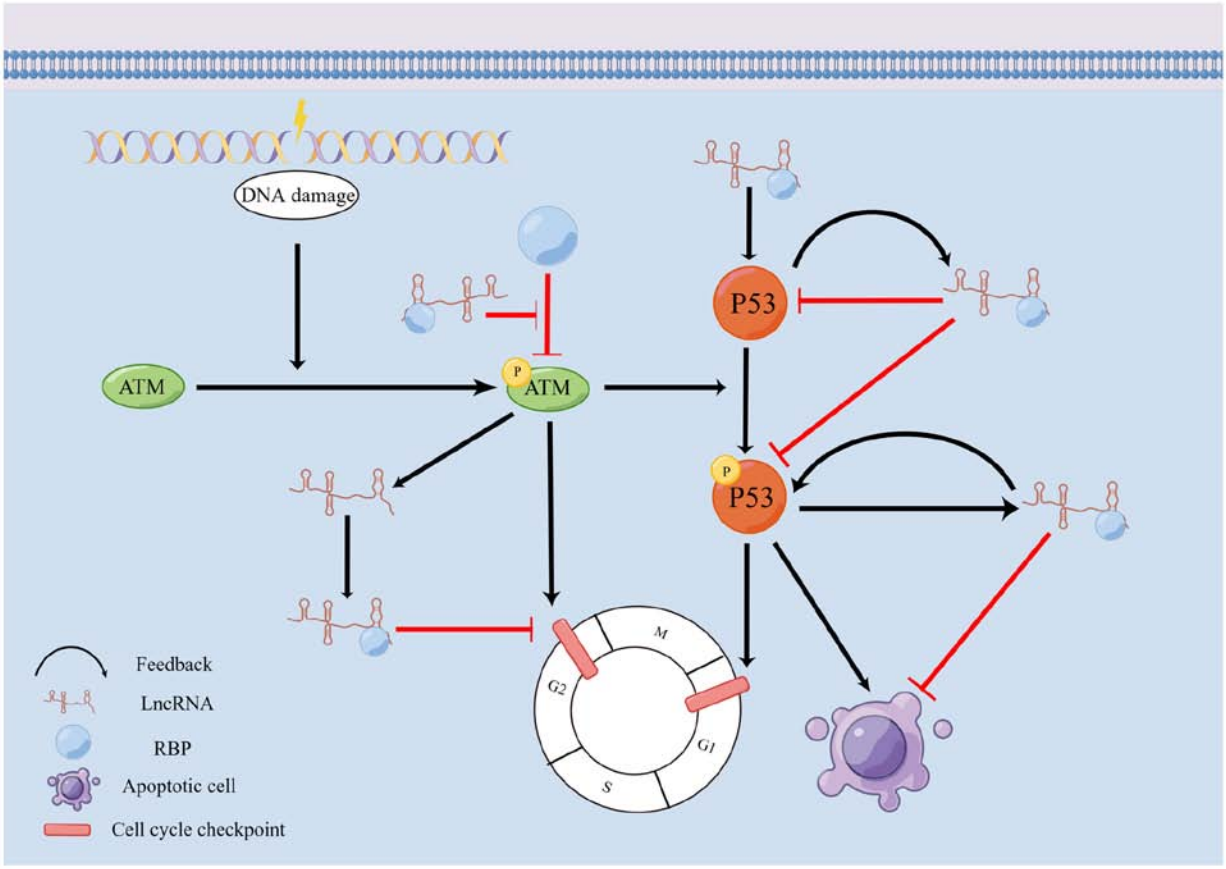

Figure 1. lncRNAs are involved in the regulation of the DNA damage response by binding to RBPs to regulate cell cycle checkpoints and apoptosis. The activation of ATM following DNA damage induces the production of lncRNAs and the binding to RBPs inhibits cell cycle checkpoint activation and promotes cell proliferation; the binding of lncRNAs to RBPs interferes with the pathway that inhibits cell cycle checkpoint activation and inhibits cell proliferation. lncRNA binding to RBPs interferes with pathways that inhibit ATM activation, thereby activating cell cycle checkpoints and inhibiting cell proliferation. lncRNA binding to RBPs promotes or inhibits p53, thereby regulating p53-mediated cell cycle arrest and apoptosis, and p53 promotes lncRNA production, forming a feedback regulation. p53 activation induces lncRNA production and binding to RBPs, inhibiting apoptosis; lncRNAs bind RBPs to regulate p53 transcriptional response and promote apoptosis. lncRNAs, long non-coding RNAs; RBPs, RNA binding proteins; ATM, ataxia telangiectasia mutated. The figure was drawn using Figdraw (www.figdraw.com).

p53. p53 is a crucial transcription factor involved in stress and the DDR. It plays a pivotal role in activating cell cycle arrest, DNA repair and apoptosis (42). In non-stressed cells, p53 levels are maintained at low levels, while p53 levels are significantly increased during stress (43). In response to stress signals such as DNA damage, p53 is stabilized and activated to perform its function as a sequence-specific transcription factor, inducing genes involved in cell cycle arrest, apoptosis and the expression of its negative regulators (44,45). Apart from protein-coding genes, an increasing number of lncRNAs are recognized as targets of p53 and contribute to p53 regulation and its effector functions (46). lncRNAs can also be involved in the regulation of p53 function through their interactions with RBPs, thereby influencing the DDR.

Inhibition and activation of P53. Zhang *et al* (42) discovered that following DNA damage, lncRNA ROR interacted with phosphorylated hnRNP I in the cytoplasm. This interaction disrupted the binding of hnRNP I to p53 mRNA, leading to the inhibition of p53 translation. Consequently, p53-mediated cell cycle arrest and apoptosis were suppressed (42). Moreover, p53 forms a self-regulatory feedback loop by regulating ROR and inducing its production. This negative feedback regulation allows for better cellular adaptation to intracellular or extracellular stress (42). Shihabudeen Haider Ali *et al* also observed that lncRNA Meg3 expression was induced in a p53-dependent manner following DNA damage. p53-dependent lncRNA Meg3 was found to interact with the RBP PTBP3, which inhibited the activation of p53 and suppressed the p53 signaling pathway. This interaction played a role in modulating the DDR (47). In cervical cancer cells, Wen *et al* (48) found that Linc02535 collaborated with PCBP2 in the cytoplasm to inhibit the nuclear translocation of p53. This led to the promotion of cell cycle progression, DNA damage repair, inhibition of apoptosis and the enhancement of cell proliferation. These events were shown to contribute to the development of cervical cancer *in vivo* (48). By contrast, Li and Richard (49) discovered that PR-lncRNA-1 interacted with Sam68, enhancing the binding of Sam68 to p53. The presence of Sam68 enhanced the DNA damage-induced expression of PR-lncRNA-1, which in turn promoted the loading of Sam68 and p53 onto the target promoter (49). This upregulation of PR-lncRNA-1 forms a positive feedback regulatory mechanism and enhances p53-mediated cell cycle arrest and the apoptotic regulation of the DDR (49).

p53 transcriptional response. The transcriptional response of p53 involves the activation and repression of numerous genes. It has been discovered that lncRNAs play crucial regulatory roles in the p53 transcriptional response (50). Huarte *et al* (51) reported that lincRNA p21, located upstream of the CDKN1A gene, was activated by p53 following DNA damage. lincRNA P21 interacted with hnRNPK to participate in a p53-dependent transcriptional repression response. It inhibited the expression of downregulated genes that are typically part of the p53 transcriptional response, thereby promoting apoptosis and contributing to the regulation of the DDR (51). By contrast, Hung *et al* (52) found that an lncRNA termed PANDA, induced in a p53-dependent manner, restricted apoptosis in the DDR. PANDA was found to bind to NF-YA, preventing or repelling NF-YA from binding to chromatin. This suppression of NF-YA binding led to the downregulation of pro-apoptotic genes, cell cycle arrest and the subsequent regulation of the DDR (52).

3. lncRNA binding to RBPs regulates DNA DSB repair in cancer cells

DNA repair is a critical biological process that ensures the integrity of genomic DNA and enables normal physiological functions, such as cell division (10,53). Under normal conditions, cells possess six major DNA repair pathways that precisely repair DNA damage, thus maintaining genomic stability (54). Among the various types of DNA damage, DSBs are particularly harmful and challenging to repair (55). Fortunately, cells have two primary pathways for repairing DSBs: HR and NHEJ (56). These pathways are typically mediated by proteins belonging to the phosphatidylinositol 3-kinase-like protein kinase family, such as ATM, ATM- and Rad3-related (ATR), and DNA-dependent protein kinase catalytic subunits (DNA-PKcs) (10). The selection of the repair pathway is influenced by the cell cycle phase (57). In the G1 phase, DSBs are primarily repaired through error-prone NHEJ, involving the direct rejoining of DNA ends (58). By contrast, during the S/G2 phase, HR becomes the predominant pathway and utilizes homologous DNA template sequences for error-free repair (59). HR is considered more conserved and error-free due to its reliance on sister chromatids (60,61). However, this property restricts the ability of the HR pathway to repair DSBs to the S/G2 phase, while the NHEJ pathway can repair DSBs throughout the cell cycle (62-64).

The regulatory mechanisms of DNA damage repair play a critical role in the identification of tumor markers and the development of more effective targeted therapies. While the functions of lncRNAs have been extensively studied (65), only a limited number of lncRNAs have been implicated in DNA repair processes (66-68). Furthermore, lncRNAs can bind to RBPs to regulate DNA damage repair. Therefore, it is essential to investigate the regulatory mechanisms involving lncRNAs and RBPs in the two repair pathways, HR and NHEJ, specifically in DSB repair (Fig. 2 and Table II).

NHEJ pathway. The NHEJ pathway is an error-prone mechanism initiated by the binding of DNA break ends to DNA-PK complexes (69). Upon encountering DNA DSBs, Ku80-Ku70 heterodimers bind to the broken ends, forming a clamp complex that recruits DNA-PKcs to the injury site. Two DNA-PKcs molecules interact with the DSB site, forming a synaptic complex that immobilizes the DSB end and protects it from nuclease digestion. Following DNA end processing by Artemis, DNA ligase (LIG)4 and XRCC4 mediate DNA ligation to facilitate the repair of the broken ends (70).

Ku is an RBP that stabilizes the initial synaptic complex in classical NHEJ DSB repair (71). lncRNAs can regulate this repair pathway by binding to Ku. Zhang *et al* (72) discovered that in triple-negative breast cancer, lncRNA LINP1 interacted with Ku80 and DNA-PKcs, acting as a molecular scaffold. This interaction enhanced the molecular interactions between Ku80 and DNA-PKcs, stabilized the Ku80-DNA-PKcs complex and promoted NHEJ-mediated DNA repair (72). Similarly,

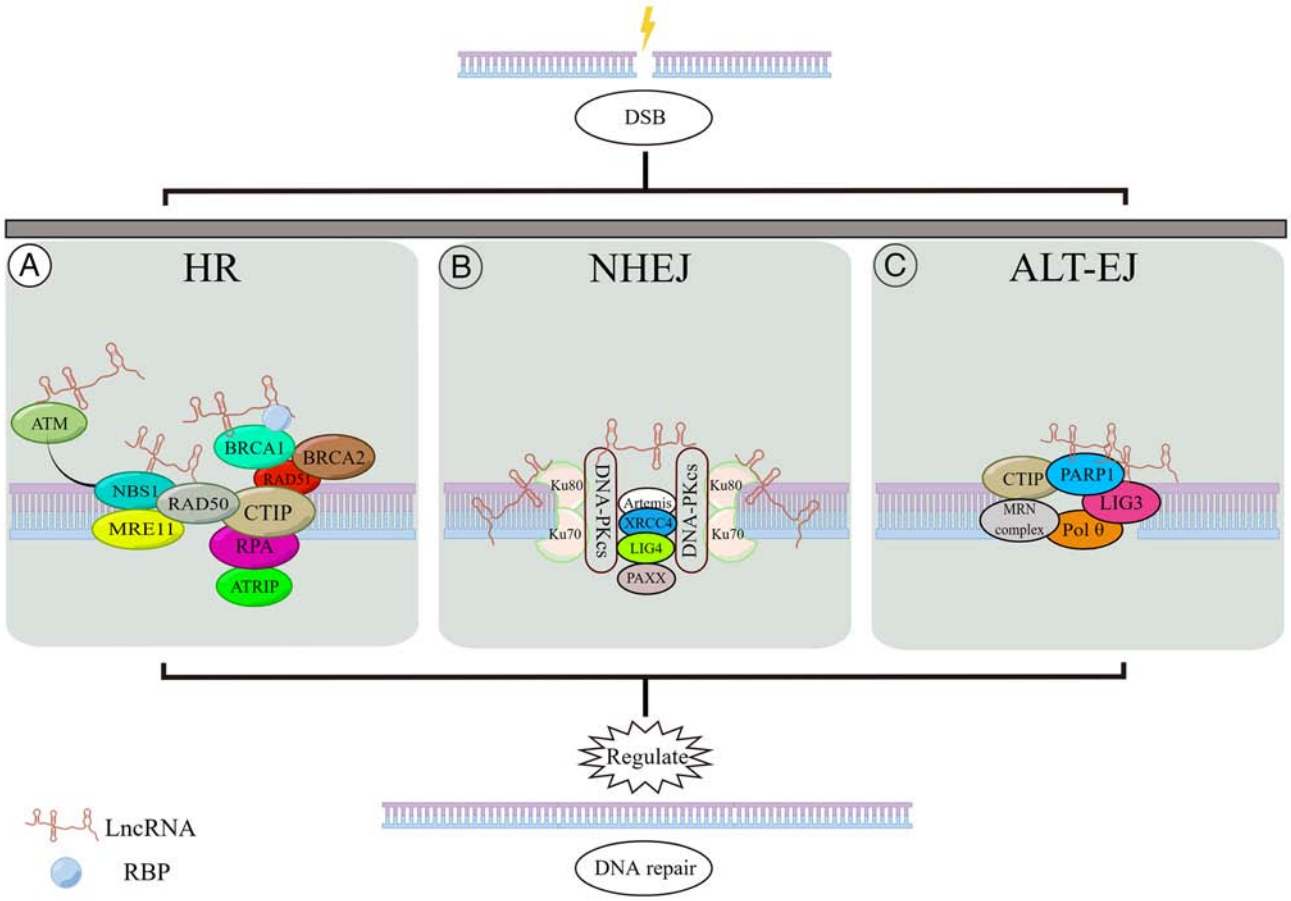

Figure 2. lncRNAs are involved in the regulation of different DSB repair pathways through binding to RBPs. (A) lncRNA binding to RBPs affects the recruitment of repair factors in HR repair pathways, regulate the formation of MRN complexes, etc., which in turn regulate the repair of DNA DSBs. (B) lncRNA binding to RBPs affects the interaction and recruitment of repair factors in the NHEJ repair pathway, etc., and thus regulate repair of DNA DSBs. (C) lncRNA binding RBPs regulates DNA repair by affecting DNA DSBs recognition sites, etc. lncRNAs, long non-coding RNAs; RBPs, RNA binding proteins; DSBs, double-strand break; NHEJ, non-homologous end joining; HR, homologous recombination; ALT-EJ, alternative end joining; ATM, ataxia telangiectasia mutated; NBS1, Nijmegen breakage syndrome 1 protein; MRE11, meiotic recombination 11 homolog 1; RAD50, ATP-binding cassette-ATPase; BRCA1, breast cancer type 1 susceptibility protein; BRCA2, breast cancer type 2 susceptibility protein; CTIP, C-terminal-binding protein interacting protein; RPA, replication protein A; ATRIP, ATR interacting protein; DNA-PKcs, DNA-dependent protein kinase catalytic subunits; XRCC4, X-ray repair cross-complementing protein 4; LIG4, DNA ligase 4; PAXX, MRN complex, MRE11-RAD50-NBS1 complex. The figure was drawn using Figdraw (www.figdraw.com).

in patients with cervical cancer, Wang *et al* (73) observed the elevated expression of lncRNA LINP1, which promoted NHEJ-mediated DNA repair through the same mechanism described above. Thapar *et al* (71) further revealed that the interaction between LINP1 and Ku effectively substituted the auxiliary NHEJ protein PAXX in the NHEJ complex. LINP1 enhanced NHEJ-mediated DNA repair by increasing the net concentration of NHEJ factors at DSBs and facilitating the joining of two Ku heterodimers via DSBs, thereby effectively replacing PAXX and achieving efficient NHEJ (71). The early and long-term binding of repair factors has been shown to play a crucial role in the initiation and signal transduction of DNA damage and repair (74). Repair factors, including DNA-PKcs, XRCC4, LIG4 and XLF, bind to DSBs following the perception of damage by the Ku70-Ku80 heterodimer (75). In various cancer cells, lncRNA LRIK is upregulated upon the induction of DNA damage. LRIK interacts with Ku70-Ku80 heterodimers, prolonging their binding to DSB sites and promoting the recruitment of XRCC4 and DNA-PKcs, thereby enhancing the formation of repair complexes at DSB sites in chromatin and facilitating effective DNA damage repair through the NHEJ pathway (76). By contrast, the study by Guo *et al* (77) reported that linc00312 expression was downregulated in nasopharyngeal carcinoma, leading to a significant decrease in patient survival. Further investigations revealed that linc00312 directly bound to DNA-PKcs and inhibited its recruitment to Ku80, thereby impairing NHEJ repair (77). This, in turn, reduced the viability of nasopharyngeal carcinoma cells and promoted apoptosis (77).

HR pathway. Upon DNA damage, the meiotic recombination 11 homolog 1 (MRE11)-RAD50-Nijmegen breakage syndrome 1 protein (NBS1) (MRN) complex acts as a sensor for DNA DSBs and binds to the damaged site. BRCA1 and CTIP are subsequently recruited to the site of damage. The MRN complex facilitates the activation of ATM through autophosphorylation (78,79). Activated ATM phosphorylates various DNA repair factors, including core histone variants H2AX, CTIP, BRCA1, and the exonuclease EXO1 (59). BRCA1 interacts with CTIP, leading to the activation of MRE11 and stimulating the exonuclease and endonuclease activities necessary for excising the 5'-3'DNA strand and generating

Table II. lncRNAs bind to RBPs to regulate DSBs repair.

lncRNA	RBP	Mechanism	Role	(Refs.)
LINP1	Ku80 and DNA-PKcs	Enhancement of molecular interaction between Ku80 and DNA-PKcs and stabilization of Ku80-DNA-PKcs complexes	Promote NHEJ	(72)
	Ku heterodimer	Replaces the auxiliary NHEJ protein PAXX in the NHEJ complex	Promote NHEJ	(71)
LRIK	Ku heterodimer	Enhanced formation of repair complexes at DSB sites in chromatin	Promote NHEJ	(76)
Linc00312	DNA-PKcs	Inhibition of the recruitment of DNA-PKcs to Ku80	Inhibition of NHEJ	(77)
DDSR1	hnRNPUL1 and BRCA1	Isolates the formation of BRCA1-RAP80 complex, derepresses DNA end resection, and regulates the recruitment of BRCA1 and RAP80 to DSB	Promote HR	(55)
BGL3	PARP1	BRCA1/BARD1 complex retention at the DSB site and enhanced RAD51 recombinase activity regulates DNA end resection	Promote HR	(91)
ANRIL-L	EZH2 and Ring1B	Recruiting BRCA1, BRCA2, RAD50, and RAD51 proteins	Promote HR	(92)
H19	RBBP8	Involvement of MRN complexes in DNA end resection	Promote HR	(95)
HITTERS	RAD50 and MRE11	Promote the formation of MRN complexes	Promote HR	(96)
PRLH1	RNF169	Formation of a stable repair complex that replaces 53BP1 at the DSB site	Promote HR	(56)
HITT	ATM	Masking the site on ATM that binds to NBS1 prevents NBS1-mediated recruitment of ATM to the DSB	Inhibition of HR	(98)
MALAT1	PARP1 and LIG3	Promoting PARP1/LIG3 complex recognition of DSB γH2AX sites on DNA	Promote A-NHEJ	(108)

lncRNA, long non-coding RNA; DNA-PKcs, DNA-dependent protein kinase catalytic subunits; NHEJ, non-homologous end joining; HR, homologous recombination; DSB, double-strand break; BRCA1, breast cancer type 1 susceptibility protein; PARP1, poly(ADP) ribose polymerase 1; MRN complex, MRE11-RAD50-NBS1 complex; ATM, ataxia telangiectasia mutated; NBS1, Nijmegen breakage syndrome 1 protein; LIG3, DNA ligase 3; H2AX, H2A histone family member X.

a 3'single-stranded DNA (ssDNA) overhang. The ssDNA is then coated by replication protein A (RPA), which prevents the formation of DNA secondary structures. The RPA-coated ssDNA activates CHK1 and CHK2 through ATRIP, resulting in cell cycle arrest to allow time for repair (79-82). BRCA2 binds to BRCA1 and promotes the recruitment of RAD51 to the RPA-coated ssDNA, displacing RPA and forming a stable RAD51-ssDNA complex. BRCA2 also inhibits the ATPase activity of RAD51 and stabilizes the RAD51-ssDNA complex (10,79,83,84). Subsequently, a homology search and DNA repair through strand invasion take place (85).

BRCA1 plays a critical role in the HR repair of DNA (86). Its accumulation at the DNA damage site is essential for an appropriate response to DSBs (24). DNA end resection is a crucial step in initiating and facilitating HR, while inhibiting NHEJ (85). However, BRCA1 can interact with the ubiquitin-binding protein, receptor-associated protein 80 (RAP80), and recruit to the DSB (87), and the aberrant activity of this BRCA1-RAP80 complex would limit HR repair by inhibiting DSB end resection (88-90). Sharma *et al* (55) reported that following induction by DNA damage, lncRNA DDSR1 interacted with hnRNPUL1 and regulated the formation of the BRCA1-RAP80 complex. This interaction derepressed DNA end resection and regulated the recruitment of BRCA1 and RAP80 at the DSB site, thereby promoting HR repair. The deletion of DDSR1, on the other hand, impaired HR repair (55). Similarly, Hu *et al* (91) induced DNA damage in breast cancer cell lines and observed that lncRNA BGL3 interacted with poly(ADP-ribose) polymerase 1 (PARP1). Upon recruitment of BGL3 to the DNA damage site, it bound to BARD1 and facilitated the interaction of the BRCA1/BARD1 complex with its binding partners (e.g., RAD51). This resulted in the retention of the BRCA1/BARD1 complex at the DSB site and enhanced RAD51 recombinase activity, which regulated DNA end resection and promoted HR repair (91). In pancreatic cancer cell lines, two isoforms of the lncRNA ANRIL exist, one of which is ANRIL-L, which binds to DNA damage sites and forms a complex with EZH2 and Ring1B. This complex recruits BRCA1, BRCA2, RAD50 and RAD51 proteins to facilitate DNA HR repair during DNA damage repair processes (92).

The MRN complex plays a central role in DNA damage repair by sensing damaged DNA, processing broken DNA ends, and activating DNA damage repair pathways (93,94). In osteosarcoma, lncRNA H19 interacts with RBBP8 (also known as CTIP) and participates in the MRN complex in DNA end resection, promoting HR-mediated DSB repair (95). Under endoplasmic reticulum stress, HITTERS interacts with both RAD50 and MRE11, promoting the formation of MRN complexes. This interaction increases the expression

of proteins involved in DNA damage repair, facilitates the repair of the HR pathway, protects oral squamous cell carcinoma from endoplasmic reticulum stress-induced apoptosis, and promotes cancer development (96). MRN complexes also contribute to ATM phosphorylation, subsequently triggering the phosphorylation of various ATM effector proteins (97). Zhao *et al* (98) reported that lncRNA hypoxia inducible factor-1α (HIF-1α) inhibitor at translation level (HITT) was induced and maintained at high levels following DSB in HCT116 cells. HITT bound to the NBS1 binding site in ATM, masking the site on ATM that binds to NBS1 (98). This binding inhibited the association between ATM and NBS1, preventing the NBS1-mediated recruitment of ATM to the DSB and inhibiting HR repair. This highlights the potential role of HITT in sensitizing cancer to genotoxic treatment (98).

During the G1 phase of the cell cycle, the 53BP1 protein blocks the accumulation of BRCA1 at the DSB site and promotes NHEJ (99-101). The E3 ubiquitin ligase RNF169 has been found to replace 53BP1 at the DSB site, facilitating the initiation of HR repair (102,103). Deng *et al* (56) discovered that lncRNA PRLH1 specifically bound to RNF169 via two GCUUCA boxes in its 5'terminal region, forming a stable repair complex. This complex stabilized RNF169 and controled the recruitment and retention of RNF169 at the DSB site, replacing 53BP1 and facilitating HR repair (56).

Alternative end joining (ALT-EJ) pathway. In addition to the NHEJ and HR pathways, an alternative end-joining repair pathway, known as ALT-EJ or microhomologous gene-mediated end joining, is responsible for the repair of residual DSBs that cannot be resolved by NHEJ or HR. ALT-EJ is associated with frequent chromosomal abnormalities, such as deletions, translocations, inversions and complex rearrangements (104). It is Ku-independent and is dependent on the microhomologous regions on either side of the break site (70). Several proteins have been identified to be involved in the ALT-EJ repair pathway in mammals, including CTIP in complex with MRN, PARP1, LIG3 and DNA polymerase Pol θ (105). Although LIG3 lacks an RNA-binding structural domain, it can interact with PARP1 through the presence of the PARP and DNA-ligase Zn-finger (zf-PARP) region (106). PARP1 and LIG3 are key molecules in the ALT-EJ DNA repair pathway (107). Hu *et al* (108) reported that in multiple myeloma, lncRNA MALAT1 bound directly to PARP1 and indirectly to LIG3, facilitating the recognition of DSBs γH2AX sites on DNA by the PARP1/LIG3 complex and promoting DNA repair via A-NHEJ (108). It is worth noting that PARP1 has three zinc finger structural domains, with only the Zn3 structural domain capable of binding to RNA (109). Huang *et al* (110) further demonstrated in NSCLC cells that PARP1 bound to MALAT1 through the Zn3 structural domain, thereby regulating the ALT-EJ repair pathway. Additionally, MALAT1 was found to promote the HR pathway by regulating the expression of BRCA1 for DNA repair (110).

In summary, lncRNAs play a significant role in various DSB repair pathways through their interactions with RBPs, influencing cancer progression. Therefore, further investigations into the regulation of DSB repair in cancer by lncRNAs binding to RBPs are warranted.

4. Impact of DNA damage/repair on chemotherapy and radiation therapy for cancer

Resistance to chemotherapy and radiation therapy remains a significant challenge in clinical cancer treatment. DNA damage serves as a fundamental mechanism of action for these treatments. DSBs represent the most harmful form of DNA damage that can arise from radiotherapy or DNA-based chemotherapy (15). While radiation and chemotherapy are designed to induce substantial DNA damage in cancer cells, the activation of DNA damage repair systems in the body can limit their effectiveness (111). Therefore, it is crucial to investigate the effects of lncRNA binding to RBPs through DNA damage repair on chemotherapy and radiotherapy for cancer (Table III).

Influencing cancer cell chemotherapy and radiotherapy through transcriptional and post-transcriptional regulation. lncRNAs play a significant role in the regulation of various physiological and pathological cellular processes at three distinct levels: Transcriptional, post-transcriptional and epigenetic. Moreover, they are closely associated with the development, progression and prognosis of cancer (112). There is increasing evidence to support the association between lncRNAs and resistance to chemotherapy and radiotherapy in cancer treatment, thereby highlighting the potential of lncRNAs as biomarkers (113-115). One mechanism by which lncRNAs exert their functions is through their interaction with specific binding proteins (77). Taking into account the existing literature, lncRNAs combined with RBPs are mainly discussed herein to regulate DNA damage repair through transcriptional and post-transcriptional levels, which in turn affects cancer cell chemotherapy and radiotherapy. The epigenetic regulation is not further discussed.

Regulation of transcriptional levels. The CDKN1A (p21) gene plays a critical role in cell cycle checkpoint control and facilitates cell cycle arrest (116). Liu *et al* (117) discovered that in gastric cancer, lncRNA PANDAR was overexpressed and competitively bound to p53 protein, leading to the suppression of CDKN1A gene transcription. This response to DNA damage inhibited apoptosis, promoted gastric cancer cell proliferation and contributes to chemoresistance. The depletion of PANDAR combined with a p53 activator demonstrated notable efficacy in cancer therapy *in vivo* (117). PANDAR emerged not only as a potent diagnostic biomarker for patients with gastric cancer, but also as a promising target for cancer therapy (117). Additionally, TROY has been identified as a contributor to DNA damage repair (118). lncRNA SNHG8 exhibits an upregulated expression in multiple types of cancer (119-123). Zhu *et al* (124) revealed that in gastric cancer, lncRNA SNHG8 bound to hnRNPA1, leading to the stabilization of TROY expression. This interaction promoted DNA damage repair, inhibited apoptosis and ultimately promoted chemotherapeutic resistance in gastric cancer (124). The inhibition of SNHG8 impeded DNA damage repair and reduced the resistance of gastric cancer cells to chemotherapy, providing insight into a novel molecular mechanism underlying drug resistance in gastric cancer (124). Furthermore, in hepatocellular carcinoma, linc01134 has been shown to interact with the IGF2BP2 protein, enhancing MAPK1

Table III. lncRNAs bind to RBPs to influence cancer chemotherapy and radiotherapy.

lncRNA	RBP	Mechanism	Role	(Refs.)
PANDAR	p53	Repression of CDKN1A gene transcription, coping with DNA damage	Inhibits apoptosis and promotes cancer cell proliferation and chemotherapy resistance	(117)
SNHG8	hnRNPA1	Stabilization of TROY expression, promotes DNA damage repair	Inhibits apoptosis and promotes chemotherapy resistance	(124)
LUCAT1	PTBP1	Regulation of selective splicing of downstream target genes (APP, CD44, CLSTN1, MBNL1 and ZNF207), inhibits DNA damage	Inhibits apoptosis and promotes chemotherapy resistance	(130)
lnc-POP1-1	MCM5	Inhibition of MCM5 protein ubiquitination to slow down degradation, promotes DNA damage repair	Promotes chemotherapy resistance	(135)
AL133467.2	ZCCHC4 and γH2AX	Downregulation of DNA damage intensity in cancer cells and inhibition of DNA damage-induced apoptosis	Inhibits apoptosis and promotes chemotherapy resistance	(140)
HITT	ATM	Masking the site on ATM that binds to NBS1, preventing NBS1-mediated recruitment of ATM to DSBs, inhibition of HR pathway repair	Leads to increased cell death and promotes chemotherapy sensitivity	(98)
Linc01134	IGF2BP2	Enhancement of MAPK1 mRNA stability and promotion of MAPK1 expression, regulating DNA damage response	Inhibits apoptosis, promotes cancer cell proliferation and radiotherapy resistance	(125)
NORAD	PUM1	Promotion of EEPD1 expression, enhances DNA double-strand break repair	Inhibits apoptosis and promotes resistance to radiotherapy	(126)
MALAT1	ANKHD1	Positive regulation of YAP1 transcriptional activity, promotes DNA double-strand break repair	Promotes cell proliferation and resistance to radiotherapy	(128)
LINP1	Ku80 and DNA-PKcs	Enhanced NHEJ-mediated DNA repair activity on DNA double-strand breaks	Increases the survival rate of cancer cells and confers resistance to radiotherapy	(72)
Linc00312	DNA-PKcs	Inhibition of DNA-PKcs recruitment to Ku80 and inhibition of NHEJ repair pathway	Decreases cancer cell viability, promotes apoptosis, and enhances radiotherapy sensitivity	(77)

lncRNA; long non-coding RNA; PTBP3, polypyrimidine tract binding protein 3; MCM5, minichromosome maintenance deficient 5; H2AX, H2A histone family member X; ATM, ataxia telangiectasia mutated; IGF2BP2, insulin-like growth factor 2 mRNA binding protein 2; PUM1, Pumilio homolog 1; ANKHD1, ankyrin repeat and KH domain containing 1; DSB, double-strand break; DNA-PKcs, DNA-dependent protein kinase catalytic subunits; NHEJ, non-homologous end joining.

mRNA stability and promoting MAPK1 expression, regulating DDR (125). This interaction inhibits apoptosis, accelerates cancer cell proliferation, and augments radiotherapy resistance. Consequently, linc01134 may represent a potential therapeutic target for enhancing the effectiveness of radiotherapy in hepatocellular carcinoma (125). Similarly, Sun *et al* (126) reported that the DNA damage-activated non-coding RNA NORAD competitively bound to PUM1 of pri-miR-199a1, impeding the processing of pri-miR-199a1. Consequently, the expression of miR-199a-5p was suppressed, resulting in the upregulation of EEPD1 expression (126). This process enhanced the HR repair pathway in DNA DSBs and inhibited cell apoptosis, thereby conferring resistance to radiotherapy in ESCC cells (126). Previous research by Yao *et al* (127) demonstrated that ANKHD1 was highly expressed in colorectal cancer (CRC) and promoted CRC cell proliferation, invasion and migration through the activation of YAP1. Subsequent investigations revealed that ANKHD1 interacted with both lncRNA MALAT1 and YAP1 in CRC. Both ANKHD1 and MALAT1 positively regulated the transcriptional activity of YAP1, which in turn promoted ATM-CHK2 phosphorylation by activating AKT. Consequently, this cascade upregulated MRE11 expression, facilitating DNA DSB repair and ultimately promoting radiotherapy resistance in CRC. This ANKHD1/MALAT1/YAP1 interaction loop, along with the downstream YAP1/AKT axis, may represent a potential therapeutic target for comprehensive CRC treatment (128).

Post-transcriptional regulation. lncRNAs can exert their influence on resistance to chemo- and radiotherapy in cancer cells through post-transcriptional regulation. PTBP1 is an RBP known for its involvement in premature RNA splicing events and its association with cancer progression (129). Huan *et al* (130) discovered that in CRC, lncRNA LUCAT1 was induced by HIF-1α transcription under hypoxic stress. Elevated levels of LUCAT1 interacted with PTBP1 protein, regulating the selective splicing of downstream target genes (APP, CD44, CLSTN1, MBNL1 and ZNF207) (130). This interaction inhibited DNA damage and apoptosis, leading to chemoresistance and promoting CRC cell survival. These findings suggest that LUCAT1 may serve as a predictive indicator and therapeutic target for patients with CRC undergoing chemotherapy (130).

Influencing cancer cell chemotherapy and radiotherapy by regulating the repair of DNA DSBs. Resistance to chemotherapy and radiotherapy primarily arises from the induction of DNA DSBs. In response, three important DNA damage sensors, ATM, ATR and DNA-PKcs, are immediately activated to assist cancer cells in evading the damage caused by chemo- and radiotherapy. This evasion is accomplished through enhanced DNA repair mechanisms (131-133). Zhang *et al* (72) reported that LINP1 was highly expressed in triple-negative breast cancer and that the inhibition of LINP1 expression impaired DNA repair activity, thereby sensitizing the cancer cells to radiation therapy. Their study also revealed a positive correlation between LINP1 and epidermal growth factor receptor (EGFR) expression (72). Further investigations demonstrated that EGFR pathway activation, followed by MAPK (RAS-MEK-ERK) pathway activation and AP1 transcription factor induction, led to an increased LINP1 transcription (72). Elevated LINP1 levels stabilized the interaction between Ku80 and DNA-PKcs, enhancing NHEJ-mediated DNA repair activity. This, in turn, increased cancer cell survival and contributed to radiotherapy resistance (72). Similar mechanisms have been observed in cervical cancer, where LINP1 played a role in radiation resistance and served as a prognostic marker and potential therapeutic target (73). Conversely, another study demonstrated that linc00312 expression was downregulated in nasopharyngeal carcinoma and this was associated with a reduced patient survival (77). Subsequent analyses demonstrated that linc00312 directly bound to DNA-PKcs, inhibiting its recruitment to Ku80 and impairing NHEJ repair. This resulted in the decreased viability and increased apoptosis of nasopharyngeal carcinoma cells (77). Moreover, linc00312 inhibited radiation-induced AKT-DNA-PKcs, MRN-ATM-CHK2 and ATR-CHK1 signaling, leading to impaired DNA damage sensing, processing and repair. Consequently, the sensitivity to radiation therapy was increased. These findings provide new insight into the regulation of radiosensitivity by linc00312 in nasopharyngeal carcinoma (77). Additionally, Zhao *et al* (98) reported that lncRNA HITT was downregulated in multiple types of cancer. However, under DSB induction, HITT transcription was upregulated and maintained at high levels. HITT bound to the NBS1 binding site in ATM, preventing the association between ATM and NBS1 (98). This inhibition hindered the recruitment of ATM to the DSB site, impairing HR pathway repair. *In vitro* and *in vivo* analyses demonstrated that the HITT-mediated inhibition of ATM increased the death of cancer cells treated with doxorubicin, suggesting its significant role in enhancing chemosensitivity. Blocking the NBS1/ATM interaction may thus be a potential target for anticancer therapy (98).

Ubiquitination modifications. lncRNAs can also regulate protein levels through ubiquitination modifications (134). Jiang *et al* (135) discovered that in head and neck squamous cell carcinoma (HNSCC), upregulated lnc-POP1-1 directly bound to the DNA repair protein minichromosome maintenance deficient 5 (MCM5), which attenuated the degradation of MCM5. This interaction promoted DNA damage repair by inhibiting the ubiquitination of MCM5 protein, ultimately leading to cisplatin resistance in HNSCC cells (135). VN1R5 and Lnc-POP1-1 may thus serve as predictive markers for cisplatin resistance and potential therapeutic targets for reversing cisplatin resistance in HNSCC patients (135).

In recent years, the role of RBPs and their partners in cancer progression and treatment has garnered increasing attention (136,137). RBPs were once considered 'non-druggable'; however, the identification of small molecules or chemically modified antisense oligonucleotides targeting RBPs has opened up new possibilities for the treatment of certain diseases (138,139). Zhu *et al* (140) discovered that a highly expressed RBP, zinc finger CCHC domain-containing protein 4 (ZCCHC4), was associated with a poor prognosis in several types of cancer. ZCCHC4 and the previously unidentified lncRNA AL133467.2 formed nuclear complexes with the DNA damage indicator γH2AX in oxaliplatin-induced DDR. ZCCHC4 attenuated AL133467.2 and γH2AX, resulting in a downregulation of DNA damage intensity in cancer cells (140). This interaction inhibited DNA damage-induced apoptosis in hepatocellular carcinoma cells and promoted chemoresistance. These findings provide a novel understanding of the mechanisms through which RBPs and their interacting molecules regulate cancer progression and chemoresistance. The epigenetic role of RBPs and their partners in solid cancer chemoresistance remains poorly understood and thus requires further investigation (140).

5. Conclusions and future perspectives

DNA damage, DDR, and repair are crucial factors in cancer development, progression and therapy. Despite previous perceptions of lncRNAs as 'junk RNA' due to their lack of protein-coding capacity, it is now evident that they play significant roles in various aspects of cancer biology. lncRNAs interact with RBPs and contribute to numerous cellular processes, including the regulation of DNA damage repair in cancer cells. The present review provides insight into the molecular mechanisms underlying the interaction between lncRNAs and RBPs, specifically in the context of DNA damage repair in cancer cells. This knowledge may open up new avenues for cancer treatment strategies aimed at enhancing the effectiveness of DNA damage-repair-based therapies. Although substantial research has been conducted to elucidate the functions and mechanisms of lncRNAs and their impact on cancer therapy,

the precise underlying mechanisms remain largely unknown. Therefore, further investigations are warranted to enhance the current understanding of this intricate interplay.

Acknowledgements

Not applicable.

Funding

The present review was supported by the National Natural Science Foundation of China (grant no. 82160575) and the Outstanding Young Technological and Innovative Talent Cultivation Project of Zunyi Municipal Science and Technology Bureau, 2021 (no. 10).

Availability of data and materials

Not applicable.

Authors' contributions

SZ and KW conceived the study. SZ drafted the manuscript, and prepared the figures and tables. XG participated in the literature search and in the analysis of the data to be included in the review. KW edited and revised the manuscript. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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