Long non-coding RNAs interact with RNA-binding proteins to regulate genomic instability in cancer cells (Review)

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Abstract. Genomic instability, a feature of most cancers, contributes to malignant cell transformation and cancer progression due to the accumulation of genetic alterations. Genomic instability is reflected at numerous levels, from single nucleotide to the chromosome levels. However, the exact molecular mechanisms and regulators of genomic instability in cancer remain unclear. Growing evidence indicates that the binding of long non-coding RNAs (lncRNAs) to protein chaperones confers a variety of regulatory functions, including managing of genomic instability. The aim of the present review was to examine the roles of mitosis, telomeres, DNA repair, and epigenetics in genomic instability, and the mechanisms by which lncRNAs regulate them by binding proteins in cancer cells. This review contributes to our understanding of the role of lncRNAs and genomic instability in cancer and can potentially provide entry points and molecular targets for cancer therapies.

Contents

1. Introduction

Genomic instability refers to genetic alterations that occur at a higher-than-normal frequency and are caused by dysfunctional genome maintenance programs. The term includes changes at numerous levels, from single nucleotides to chromosomes (1), mainly in the form of microsatellite instability and chromosomal instability (CIN) (2). Genomic instability, one of the most prevalent features of human cancers, can cause cells to exhibit the cancer phenotype through mutations in oncogenes and cancer suppressor genes (3). Persistent genomic instability allows cancer cells to survive under selective pressure and adapt to their microenvironment by evolving to resist different therapies (4), and affects patient prognoses (5). Although genomic instability can promote cancer development and drug resistance, it can cause cancer cell death when genomic instability continues to increase to a limiting level; thus, genomic instability has therapeutic potential for treating cancer (5-7), and elucidating the specific regulatory mechanisms involved is of great significance. Several molecular mechanisms work together to maintain genomic stability under normal physiological conditions. For example, the precise segregation of chromosomes during mitosis and the protection of chromosome ends by telomeres ensures chromosomal stability (8,9), whereas DNA repair, the most important process in the DNA damage response, prevents genomic instability by efficiently repairing DNA damage (3,10). Dysregulation of these processes may lead to genomic instability and the development of cancer. In addition, epigenetic aberrations have been suggested as mechanisms underlying genomic instability (11).

Recent studies have shown that long non-coding RNAs (lncRNAs) are aberrantly expressed in various cancers and are involved in regulating genomic instability in cancer cells (12-14). LncRNAs are transcripts greater than 200 nt in length that do not encode proteins (15) and were considered to have no biological function (16). However, later studies have shown that some lncRNAs can encode polypeptides (17) and interact with proteins, DNA, and RNA to form functional complexes and perform a variety of functions (18). Proteins are the main partners of lncRNAs (16), and the proteins that bind to RNAs are called RNA-binding proteins (RBPs), which bind various RNAs, including lncRNAs, through their RNA-binding domains (19). This interaction between lncRNAs and RBPs plays a critical role in the genomic instability of cancer cells, and by targeting the lncRNA-RBP axis, cancer progression can be inhibited, showing some potential in cancer therapy (20-25).

The present review summarizes the involvement of lncRNAs in regulating genomic instability in cancer by binding proteins that affect mitosis, telomere function, DNA repair,

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and epigenetics. The study aimed to elucidate the regulatory networks involved in genomic instability in cancer, which may contribute to the development of novel cancer therapies. A systematic literature search using PubMed was performed. The following key words were used for the literature search: 'lncRNA', 'RBP', 'genomic instability', 'telomeres', 'mitosis', 'DNA repair', and 'epigenetic'. The articles in which lncRNAs regulate genomic instability through RBPs in cancer cells were selected.

2. LncRNAs affect chromosome instability via RBPs

As the most common form of genomic instability in cancer, CIN is present in 60-80% of human tumors (26,27). It is closely associated with the occurrence and development of human cancers. On the one hand, CIN can promote tumor metastasis and recurrence, accelerate the development of multi-drug resistance in tumors, and be associated with poorer prognoses (28). On the other hand, exceedingly high levels of CIN lead to sensitivity or even death of cancer cells after exposure to cytotoxic drugs and radiotherapy (29). Both abnormal chromosome segregation during mitosis and defects in telomere function contribute to CIN; therefore, the role of lncRNA-protein binding in these processes is reviewed (Fig. 1).

Mitosis. During mitosis, precise chromosome segregation depends heavily on the precise binding of microtubules to each sister chromatids (30). Ndc80 is directly attached to microtubules and plays a central role in stable kinetochore-microtubule junctions (31). In the case of incorrect kinetochore-microtubule binding, Aurora B, phosphorylates Ndc80, causing the kinetochore-microtubule binding to become unstable or completely lose the ability to bind to microtubules (32). Concurrently, the spindle assembly checkpoint detects the binding of the kinetochore and microtubules, and transmits an unstable binding signal to the cell cycle. By generating the mitotic checkpoint complex (MCC), it inhibits the anaphase-promoting complex/cyclosome (APC/P). Through this mechanism, mitotic cells are prevented from entering anaphase and cell division until all kinetochore microtubules are stably bound (33), thus preventing chromosome missegregation and CIN.

LncRNAs can directly or indirectly affect proteins involved in this sophisticated process through RBPs (Table I). The level of lncRNA CDKN2B-AS1 is markedly upregulated in renal clear cell carcinoma and is significantly correlated with prognosis. Xie *et al* found that CDKN2B-AS1 can bind directly to IGF2BP3 protein to stabilize it while serving as a scaffold to bind to CBP and SMYD3 epigenetic modification complexes to recruit them to the NUF2 promoter. This mechanism stimulates NUF2 transcription and enhances its cancer-promoting function (34). NUF2 is a component of human Ndc80 that is required for stable microtubule-positive end-binding sites in kinetochores; the precise stoichiometry of the Ndc80 complex may play an important role in microtubule binding (31,35). Stojic *et al* screened for lncRNA linc00899 in HeLa cells by quantifying the effect of lncRNA deletion on cell division. In this study it was determined that linc00899 maintained genomic stability by inhibiting the expression of microtubule-binding protein TPPP (a protein that stabilizes microtubule networks and its overexpression inhibits microtubule dynamics) through binding to chromatin-modifying complexes (36). Moreover, an elevated level of lncRNA CCAT2 in microsatellite stable colon cancer was revealed to prolong the half-life of BOP1 by directly binding to BOP1; overexpressed BOP1 increased the active form of Aurora B, and the direct binding of CCAT2 to Aurora B also increased active Aurora B. This was demonstrated to lead to incorrect segregation of chromosomes and the occurrence of CIN, thus promoting the progression of colon cancer. Colony formation ability and migration ability of colon cancer cells were effectively inhibited by knockout of BOP1 (20). Cdc20 and Bub3 are components of MCC, and lncRNA CRYBG3 acts as a protein decoy directly binding to Bub3, preventing Bub3 interaction with CDC20, and thus activating APC/P and promoting abnormal mitosis. This then leads to aneuploidy and the development of non-small cell lung cancer. Inhibition of CRYBG3 was revealed to reduce the ability of cancer to migrate *in vitro* and *in vivo* (21). Similarly, lncRNA NORAD induced after DNA damage in HCT116 and other human cell lines can maintain normal mitosis and chromosomal stability by binding to PUMILIO, thereby interfering with PUMILIO binding and inhibiting its target mRNAs (mainly including mRNAs such as chromosome cohesion complexes and centromere complexes) (37). In conclusion, the abovementioned evidence suggests that lncRNAs are involved in the mitotic process by binding proteins that regulate mitosis; however, the levels of induced CIN and the specific biological functions of lncRNAs in cancer require further validation.

Telomeres. Human telomeres are DNA-protein complexes present at the ends of chromosomes that consist of the non-coding DNA repeat sequence TTAGGG and shelterin complexes (TRF1, TRF2, POT1, TIN2, TPP1, and RAP1) to which they are bound. Its integrity is critical to the stability of chromosomes (38). Telomeres are subsequently shortened as cells divide due to end replication problems, and short telomeres and defects in the shelterin complex fail to protect chromosome ends leading to CIN. Cancer cells maintain telomere length via the function of telomerase and use of the alternative lengthening of telomeres (ALT) (9,39). In addition, lncRNAs also play an important role in the maintenance of telomeres via RBPs (Table II).

Telomeric repeat-containing RNA (TERRA). TERRA is a long non-coding RNA transcribed from subtelomeric- and telomeric-derived sequences containing UUAGGG repeats (40). Like telomeric DNA, TERRA can also form a G-quadruplex structure and bind to the GAR structural domain of TRF2, which is essential for TERRA localization to telomeres. In the absence of the TERRA G-quadruplex structure, telomeres bind more tightly to TRF2, which can promote the formation of the telomeric T-loop. The quinoline derivative CK-14 binds to the TERRA G-quadruplex to form a complex. This complex binds to TRF2 and acts as an allosteric regulator of TRF2, thereby preventing TRF2 from binding to telomeric DNA and ultimately initiating the DNA damage response (DDR). In addition, TERRA can bind to both the origin recognition complex (ORC) and TRF2,

Table I. LncRNAs interact with RBPs to affect mitosis.

LncRNAs	RBPs	Mechanism	Effect	(Refs.)
CDKN2B-AS1	SMYD3 and CBP	Promotes the expression of NUF2	Interferes with normal mitosis	(34)
linc00899	Chromatin-modifying complexes	Inhibits TPPP expression	Interferes with normal mitosis	(36)
CCAT2	BOP1 and Aurora B	Increases the active form of Aurora B	Interferes with normal mitosis	(20)
CRYBG3	Bub3	Inhibits the binding of Bub3 and CDC20	Interferes with normal mitosis	(21)
NORAD	PUMILIO	Inhibits the binding of PUMILIO to its target mRNA	Protects normal mitosis	(37)

LncRNAs, long non-coding RNAs; RBPs, RNA-binding proteins; CDKN2B-AS1, cyclin-dependent kinase inhibitor 2B antisense; SMYD3, SET and MYND domain-containing protein 3; CBP, CREB binding protein; CCAT2, colon cancer associated transcript 2 gene; BOP1, block of proliferation 1; NORAD, noncoding RNA activated by DNA damage.

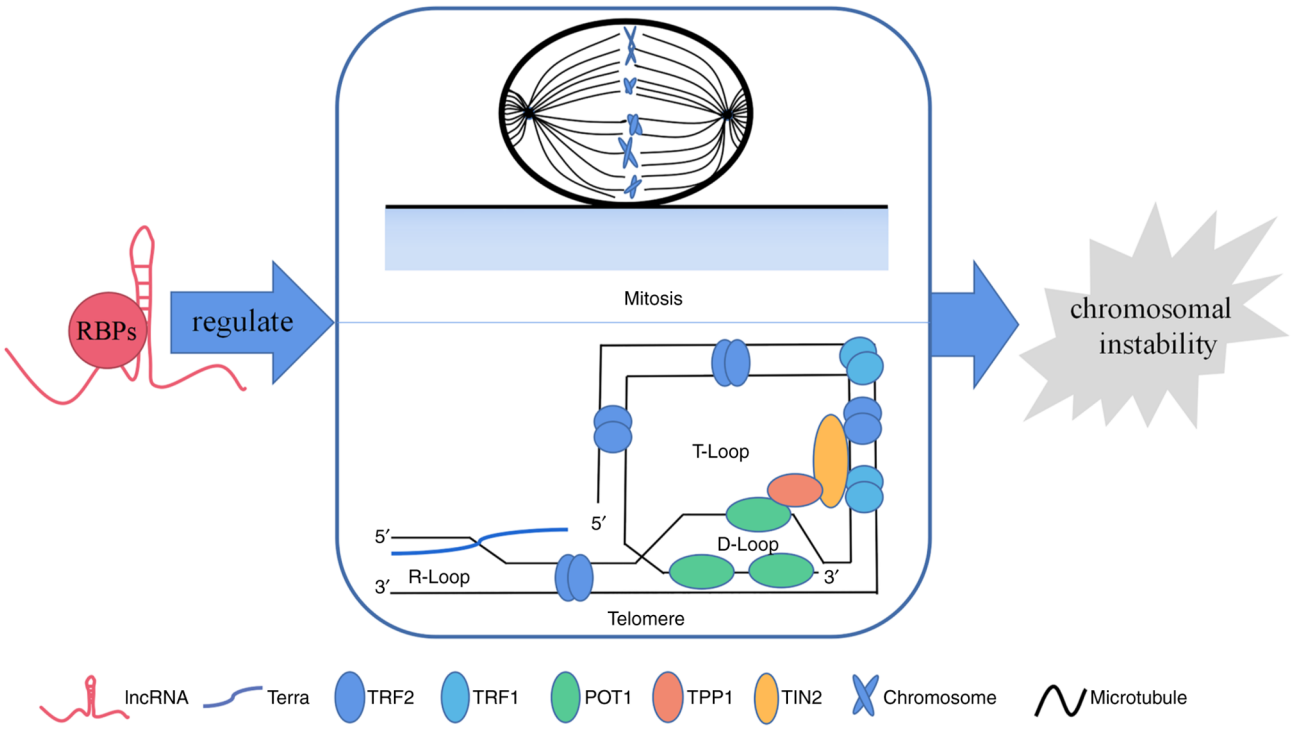

Figure 1. LncRNAs regulate mitosis and telomeres (such as telomere length, telomere capping, R-loop formation, etc.) by binding RBPs and ultimately participate in the regulation of chromosomal instability. LncRNAs, long non-coding RNAs; RBPs, RNA-binding proteins.

enabling formation of a stable ternary complex, which is involved in telomeric DNA replication and facilitates telomeric heterochromatin formation and maintenance (41-43). Similarly, translocated in liposarcoma (TLS) protein can bind to both telomeric DNA and TERRA G-quadruplex structures, while TERRA binds to histone-modifying enzymes, HP1α and β, and H3K9me3, which play important roles in telomeric heterochromatin formation (41,44). By contrast, telomeric heterochromatin is a negative regulator of telomerase and ALT elongation of telomeres (45,46). Telomeric G-quadruplexes can also regulate telomere length by preventing the binding of telomerase to telomeric DNA substrates. Previous experiments have demonstrated that hnRNP A1 can facilitate telomerase function by disrupting this high-level structure via binding to telomeric DNA (47). Interestingly, Redon *et al* determined that telomerase can only function when TERRA and hnRNP A1 levels are balanced and bound to form an inert complex. Moreover, excessive hnRNP A1 interferes with telomerase activity by binding to telomeric DNA substrates (48). In cancer cells lacking telomerase, cells maintain telomere length primarily through ALT, and the R-loop formed by telomeric DNA and

Table II. LncRNAs regulate telomere function through RBPs.

LncRNAs	RBPs	Mechanism	Effect	(Refs.)
TERRA	TRF2	Promotes the localization of TERRA in telomeres, and prevents TRF2 from binding to telomeres	Regulates telomere stability	(41,42)
	TRF2, ORC	Promotes the formation and maintenance of telomeric heterochromatin	Promotes telomere elongation	(41)
	TLS, Histone-modifying enzyme, HP1α and β	Promotes telomeric heterochromatin formation	Promotes telomere elongation	(41,44)
	HnRNP A1	Regulates telomerase activity in a dose-dependent manner	Regulates telomere length	(48)
	BRCA1	Reduces telomeric R-loop formation	Enhances telomere stability	(49)
	RAD51	Promotes telomeric R-loop formation	Reduces telomere stability	(50)
	TERT	Inhibits telomerase activity	Prevents telomere lengthening	(53)
HTR	TERT	Constitutes the main active part of telomerase	Promotes telomere elongation	(52)
	Dyskerin, NOP10, NHP2, TCAB1 and GAR1	Components of telomerase holoenzymes, maturation and localization of helper group telomerase	Promotes telomere elongation	(52)
	PinX1	Inhibits telomerase activity	Prevents telomere lengthening	(54)
	Ku70/80	Promotes telomere capping	Enhances telomere stability	(55,56)
CUDR	Cyclin D1	Promotes telomerase activity	Promotes telomere elongation	(57)
	P53 (N340Q/L344R)	Promotes telomerase activity	Promotes telomere elongation	(58)
HULC/ MALAT1	TRF2	Promotes telomere capping	Enhances telomere stability	(59)
HULC	P53	Inhibits telomere capping	Reduces telomere stability	(60)

LncRNAs, long non-coding RNAs; RBPs, RNA-binding proteins; TERRA, telomeric repeat-containing RNA; TRF2, telomeric-repeat binding factor 2; ORC, origin recognition complex; TLS, translocated in liposarcoma; HP1, heterochromatin protein 1; hnRNP A1, heterogeneous nuclear ribonucleoprotein A1; BRCA1, breast-cancer susceptibility gene 1; TERT, telomerase reverse transcriptase; hTR, human telomerase RNA; CUDR, cancer upregulated drug resistant; HULC, highly upregulated in liver cancer; MALAT1, metastasis-associated lung adenocarcinoma transcript 1.

TERRA facilitates this process. BRCA1 binds directly to TERRA in an R-loop-dependent manner and reduces R-loop formation; interference with its binding leads to increased R-loops and telomere abnormalities. By contrast, RAD51 can promote R-loop formation by binding TERRA (49,50). Thus, TERRA plays an important role in various aspects of telomere protein capping, heterochromatin formation, secondary structure formation, and telomere lengthening. Owing to the complex role of TERRA in telomeres, targeting its secondary structure or binding proteins may be useful for cancer therapy.

hTR. Telomerase is a ribonucleoprotein complex consisting of an RNA component (TERC) and the catalytic subunit of telomerase reverse transcriptase (TERT) as the major active component. The mature human TERC (hTR) is 451 nucleotides long and folds into a highly conserved structural domain. It binds to TERT via CR4/CR5 and template/pseudoknot domains. The H/ACA structural domain of hTR binds to a protein complex composed of dyskerin, NOP10, NHP2, and GAR1, and facilitates hTR processing and maturation. TCAB1 binds to the CR7 structural domain of hTR to localize telomerase (51,52). TERRA can act as a natural ligand that binds directly to TERT and hTR, thereby inhibiting telomerase activity. The binding of TERRA to TERC does not depend on the presence of hTR. By contrast, PinX1, a telomerase inhibitor, acts by binding directly to hTR and TERT, but the binding of PinX1 to hTR in the intracellular environment is dependent on the presence of TERT (53,54). In addition to providing a template for telomeric DNA replication, hTR plays an important role in telomere shelterin protein capping. The Ku70/80 heterodimer and DNA-dependent protein kinase catalytic subunit (DNA-PKcs) constitute the DNA-dependent protein kinase holoenzyme. The CR7 motif of hTR interacts with KU70/80 to enhance the phosphorylation activity of hnRNPA1. The phosphorylation of hnRNPA1 increases its affinity for single-stranded telomeric DNA, thereby replacing the replication protein A (RPA) at the telomere ends. Subsequently, hnRNPA1 interacts with protein phosphorylase 2A to undergo dephosphorylation, thereby stripping it from

telomeres and allowing POT1 to bind to telomeres. The binding of POT1 ensures telomere capping and inhibits the DDR (55,56).

Other lncRNAs. In addition to TERRA and hTR, which play important roles in telomere regulation, other lncRNAs also play a role in telomere physiology. PTEN is one of the most lost tumor suppressors in human cancers. In hepatocellular carcinoma stem cells, decreased PTEN levels lead to increased binding of the lncRNA CUDR to the cell cycle protein cyclin D1; the CUDR-cyclin D1 complex then loads into the lncRNA H19 promoter region and reduces DNA methylation in the H19 promoter region, thereby enhancing H19 expression. H19 overexpression increases TERT binding to TERC while reducing TERT binding to TERRA. This process results in increased cellular telomerase activity and extended telomere length and promoting the malignant proliferation of hepatocellular carcinoma stem cells (57). P53, another tumor suppressor, is frequently mutated in cancer cells to promote cancer progression. In hepatocellular carcinoma cells, the double mutant p53 (N340Q/L344R) binds to CUDR and promotes telomerase activity and lengthening of telomeres through a cascade reaction that enhances TERT expression and reduces TERRA expression (58). In addition to regulating telomerase activity, lncRNAs aberrantly expressed in cancer are involved in telomeric protein capping. Overexpression of lncRNAs HULC and MALAT1 results in increased RNApolII and P300 loading onto the TRF2 promoter region, enhancing TRF2 transcription at the transcriptional level. The increased TRF2 binds to HULC and MALAT1 to form a complex that is loaded onto telomeres, replacing CST/AAF and recruiting telomere-associated proteins, such as POT1, pPOT1, ExoI, and SNM1B, to maintain telomere length and stability. By contrast, lncRNA MEG3 promotes the binding of HULC to p53, thereby inhibiting the binding of telomere-associated proteins to HULC and decreasing telomere stability (59,60).

3. LncRNAs are involved in DNA repair through RBPs

The genome of an organism is subjected to endogenous and exogenous damage, causing each cell to produce up to 10^5 times the amount of DNA damage per cell per day. Under normal physiological conditions, cells have six main DNA repair pathways by which DNA damage can be precisely repaired to maintain genomic stability (61-64). DNA double-strand breaks (DSBs) are the most cytotoxic type of DNA damage and require complex repair mechanisms. They are repaired by homologous recombination (HR) and non-homologous end joining (NHEJ). Both not repairing DSBs and selecting the wrong way to repair DSBs lead to genomic instability (65-67). Therefore, lncRNAs that regulate DSB repair by binding key proteins during NHEJ and HR were mainly examined (Fig. 2; Table III).

NHEJ. Classical NHEJ (cNHEJ) is the primary repair mechanism for DSBs. It does not require a homologous template, requires minor or no processing of DSB ends, and is then directly ligated by enzymatic action, making it an efficient but error-prone repair modality (68,69). In this repair process, Ku70-Ku80 first binds to the DSB and acts as a recruitment platform for other cNHEJ proteins, such as the XRCC4.

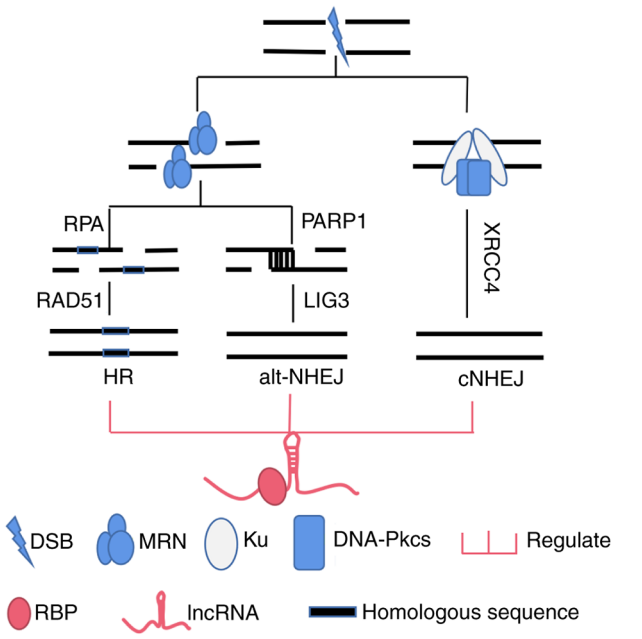

Figure 2. LncRNAs are involved in the regulation and selection of different DSB repair pathways by binding RBPs. LncRNAs, long non-coding RNAs; DSB, DNA double-strand break; RBPs, RNA-binding proteins; RPA, replication protein A; PARP1, poly ADP ribose polymerase1; HR, homologous recombination; alt-NHEJ, alternative nonhomologous end joining; cNHEJ, classical nonhomologous end joining; MRN, MRE11-Rad50-Nbs1; DNA-Pkcs, DNA-dependent protein kinase catalytic subunit.

Ku70/80 binds to DNA-PKcs activating their kinase function, which leads to the phosphorylation of Ku and other cNHEJ factors, such as Artemis. The activated Artemis allows the processing of DNA ends. Finally, end linkage is catalyzed by a complex consisting of LIG4 and XRCC4 (70,71).

Wang *et al* reported a novel lncRNA, LRIK, induced by DSB in HeLa cells, which enhances the binding of the Ku heterodimer to DSB through direct binding to the Ku70 subunit. This process promotes assembly of downstream NHEJ factors and the formation of γ-H2AX, ultimately promoting the efficiency of cNHEJ (72). Similarly, lncRNA LINP1, activated by the epidermal growth factor in triple-negative breast cancer, can be recruited to the DSB by binding directly to Ku80. LINP1 also binds to DNA-PKcs through a different region and acts as a molecular scaffold to enhance the interaction between Ku heterodimers and DNA-PKcs. This in turn enhances cNHEJ-mediated DNA repair activity and reduces cancer sensitivity to radiotherapy. Downregulation of LINP1 expression sensitizes cancer cells to radiotherapy due to defective repair activity (22). Thapar *et al* performed further studies and found that Ku binds to the LINP1 stem-loop and G-quadruplex structures (73); the Ku-LINP1 interaction replaces the NHEJ cofactor PAXX protein more efficiently, increasing the stability and net concentration of NHEJ factors at the DSB. Moreover, it bridges the Ku heterodimer at both ends of the DSB to better promote DSB end-joining (71,73). Conversely, lncRNA linc00312, which is expressed at low levels in nasopharyngeal carcinoma, can act as a protein decoy to bind to DNA-PKcs, thereby blocking the recruitment of Ku to DNA-PKcs and inhibiting cNHEJ and resistance to radiotherapy (74).

Table III. LncRNAs involved in DSB repair via RBPs.

LncRNAs	RBPs	Mechanism	Effect	(Refs.)
LRIK	Ku70	Enhances the binding of Ku heterodimer to DSB	Promotes cNHEJ	(72)
LINP1	Ku80 and DNA-PKcs	Enhances the interaction between Ku heterodimers and DNA-PKcs	Promotes cNHEJ	(22,73)
Linc00312	DNA-PKcs	Inhibits the recruitment of Ku to DNA-PKcs	Inhibits cNHEJ	(74)
MALAT1	PARP1	Promotes co-localization between LIG3 and γH2A.X	Activates alt-NHEJ	(77)
PRLH1	RNF169	Promotes RNF169 to replace 53BP1	Promotes HR and inhibits cNHEJ	(78)
SNHG17	NONO	Promotes the formation of the NHEJ repair complex	Promotes cNHEJ and inhibits HR	(79)
HITTERS	MRE11 and Rad50	Promotes the interaction between MRE11 and Rad50	Promotes HR	(82)
HITT	ATM	Prevents ATM recruitment by the MRN complex	Inhibits HR	(23)
GUARDIN	BRCA1 and BARD1	Enhances the interaction between BRCA1 and BARD1	Promotes HR	(84)
BGL3	PARP1 and BARD1	Promotes BRCA1-BARD1 retention at the DSB	Promotes HR	(85)
DDSR1	BRCA1 and hnRNPUL1	Prevents the formation of the BRCA1-RPA80 complex	Promotes HR	(86,87)

LncRNAs, long non-coding RNAs; DSB, DNA double-strand break; RBPs, RNA-binding proteins; LRIK, lncRNA interacting with Ku; cNHEJ, classical nonhomologous end joining; LINP1, lncRNA in non-homologous end joining (NHEJ) pathway 1; DNA-PKcs, DNA-dependent protein kinase catalytic subunit; MALAT1, metastasis-associated lung adenocarcinoma transcript 1; PARP1, poly ADP ribose polymerase1; alt-NHEJ, alternative nonhomologous end joining; SNHG17, small nucleolar RNA host gene 17; HR, homologous recombination; PRLH1, p53-regulated lncRNA for homologous recombination repair 1; HITTERS, HERPUD1 intronic transcript of ER stress; MRE11, meiotic recombination 11 homolog 1; RAD50, ATP-binding cassette-ATPase; HITT, HIF-1α inhibitor at translation level; ATM, Ataxia-telangiectasia mutated; BARD1, BRCA1-associated RING domain; DDSR1, DNA damage-sensitive RNA1; hnRNPUL1, heterogeneous nuclear ribonucleoprotein U-like 1.

In the case of cNHEJ damage, end linkage without the involvement of cNHEJ core factors is referred to as alt-NHEJ, as an alternate DNA repair pathway to cNHEJ that is more prone to chromosomal alterations (75,76). The alt-NHEJ pathway requires rapid recruitment of the MRN complex by poly ADP ribose polymerase1 (PARP1), which triggers end resection and is dependent on polymerase theta and LIG3 for microhomologous sequence annealing and ligation. In multiple myeloma, the lncRNA MALAT1 can bind directly to PARP1 and indirectly to LIG3. MALAT1 knockdown did not affect LIG3/PARP1 co-localization but disrupted co-localization between LIG3 and γH2A.X, suggesting that MALAT1 is important for PARP1/LIG3 complex recognition of the γH2A.X on DSB and activating alt-NHEJ repair, which promotes MM mutagenesis and drug resistance (77).

HR and NHEJ are two competing pathways in the early stages of DSB repair. The selection and balance between the two repair modalities are crucial for genomic stability (78), and lncRNAs are involved in the selection between them. Infection of normal gastric epithelial cells with *Helicobacter pylori* was demonstrated to induce high expression of lncRNA SNHG17, and lncRNA SNHG17 in the nucleus interacted directly with NONO, thus enhancing the interaction between NONO and Ku, which promoted the formation of the NHEJ repair complex. SNHG17 in the cytoplasm was shown to bind to miR-3909 as a competing endogenous RNA (ceRNA), thereby inhibiting HR, shifting the balance of DSB repair to NHEJ, and ultimately promoting gastric cancer development (79). The E3 ubiquitin ligase RNF169 can replace 53BP1, which inhibits end resection at DSB to promote NHEJ to enhance HR. In hepatocellular carcinoma, lncRNA PRLH1 can bind to RNF169 to form a stable complex that enhances the stability of RNF19 and the affinity of this protein for DSB to replace 53BP1 more efficiently, shifting the balance of repair to HR (78).

HR. Because HR is performed using sister chromatids as templates, the process occurs in the late S and G2 phases and facilitates precise repairs. The starting step of HR is the sensing of the damaged site by the MRE11-Rad50-Nbs1 (MRN) complex and producing a free 3' end single-strand overhang (80). Rad51 recombinase is the final effector of the HR cascade reaction, and its binding to single-stranded DNA depends on BRCA2 as well as the interaction of the BRCA1-BARD1 complex and PALB2. Once Rad51 binds to single-stranded DNA at the DSB, it begins the subsequent homology search and strand invasion to initiate DNA repair (81).

The lncRNA HITTERS, which is highly expressed in oral squamous cell carcinoma cells, induced by endoplasmic reticulum stress, can directly bind MRE11 and Rad50, thus promoting their interaction, while also increasing MRE11 and Nbs1 protein levels and promoting the formation of the MRN complex. Ultimately, the function of HITTERS facilitates DNA repair via multiple pathways including HR (82). Like DNA-PKcs in NHEJ, the capillary dilation ataxia mutated gene (ATM) protein kinase is the apical kinase in HR; MRN serves as a protein platform to promote autophosphorylation of ATM to stimulate its activity (83). The lncRNA HITT, which is expressed at low levels in several cancers due to hypoxic contingency, binds directly to the binding site of ATM-binding Nbs1 and thereby prevents ATM recruitment by the MRN and antagonizes HR-mediated DNA repair. Through this mechanism, overexpression of HITT can enhance the sensitivity of cancer cells to genotoxic therapies (23).

BRCA1 and BARD1 form a heterodimer, which plays a role in HR. The lncRNA GUARDIN acts as a molecular scaffold that directly binds to BRCA1 and BARD1, enhancing their interaction to promote HR (84). Similarly, lncRNA BGL3 is recruited to the DSB early by binding to PARP1, whereas direct binding to BARD1 promotes BRCA1-BARD1 retention at the DSB and facilitates the interaction between BARD1 and Rad51 (85). The lncRNA DDSR1 is known to interact with BRCA1 and hnRNPUL1; Sharma *et al* suggested that this interaction prevents the formation of the BRCA1-RPA80 complex and the binding of this complex at the DSB (86). In turn, binding of the BRCA1-RPA80 complex to the DSB restricts DNA end excision and thus limits HR (87).

Thus, lncRNAs play an important role in the different repair pathways of DSBs by binding proteins, whereas the role of lncRNAs in other repair modalities is poorly understood and warrants further investigation.

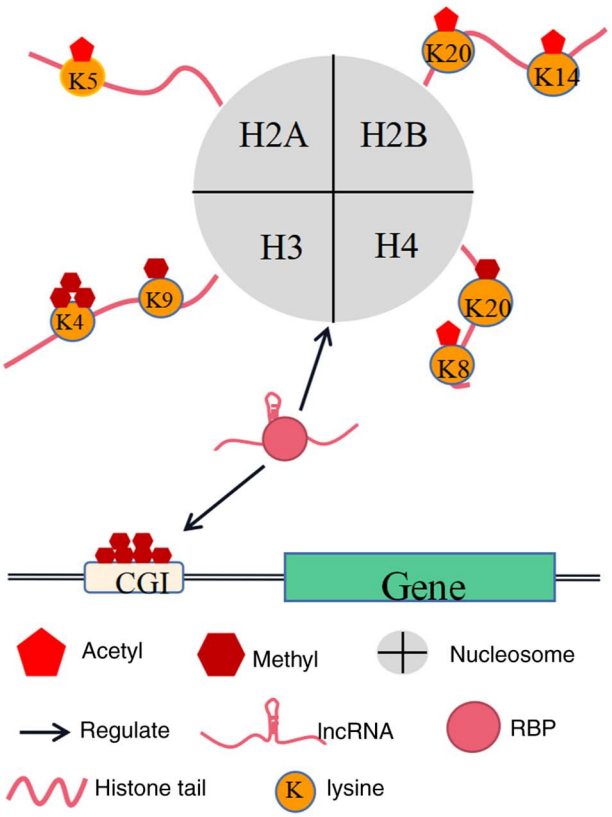

Figure 3. LncRNAs regulate gene expression by binding RBPs to regulate histone modifications and DNA methylation. LncRNAs, long non-coding RNAs; RBPs, RNA-binding proteins.

4. LncRNAs regulate other epigenetic modalities through RBPs

Epigenetic inheritance refers to the production of heritable changes in gene expression without changes to the DNA nucleotide sequence, and such epigenetic aberrations are considered a form of genomic instability. Like mutations, epigenetic inheritance plays a key role in cancer development by altering the expression of oncogenes and cancer suppressor genes (11). In addition, epigenetics may serve as an advantageous biological marker for cancer diagnosis, prognosis, and treatment. Epigenetic regulatory mechanisms mainly include DNA methylation, chromatin remodeling, and non-coding RNA (88,89). These regulatory mechanisms crosstalk: for example, lncRNAs can act as miRNA sponges to inhibit miRNAs (90). Therefore, the regulation of chromatin remodeling and DNA methylation by lncRNAs via binding to multiple enzymes (Fig. 3) was investigated.

Chromatin remodeling. The nucleosome is the basic unit of chromatin, and consists mainly of the core histones H2A, H2B, H3, and H4 that form an octamer wrapped around 147 base pairs of DNAs in humans (91); nucleosomes further assemble into higher-order chromatin (92). This highly folded state of chromatin prevents the binding of DNA-binding proteins to promoters, thereby inhibiting transcription (93). Histone-modifying enzymes and ATP-dependent chromatin remodeling complexes mediate chromatin remodeling, which controls gene expression by altering the accessibility of local chromatin DNA (93-95).

Histone modification. The amino-terminal ends of core histones can extend outside the nucleosome and be covalently modified by various histone-modifying enzymes via methylation, acetylation, ubiquitination, and phosphorylation. These modifications can affect the affinity of histones for DNA duplexes, alter the loose or condensed state of chromatin, and mediate DNA accessibility and protein-chromatin interactions, ultimately affecting gene expression (91,96,97). Methylation and acetylation are among the most intensively studied processes.

LncRNAs can play a role in cancer development by directing histone-modifying enzymes to regulate the methylation and acetylation status of histones and cis-regulating the expression of nearby genes (24,98,99). For example, lncRNA EZR-AS1 recruits H3K4 methyltransferase SMYD3 to catalyze Tri-methylation of lysine 4 on histone H3 (H3K4me3) at the EZR promoter. This process promotes EZR transcription, thereby enhancing the metastasis and invasion of the esophageal squamous cell carcinoma. Conversely, interfering with the expression of EZR-AS1 has an inhibitory effect on cancer cells (24). Similarly, lncRNAs, such as HOTAIR and

AS1DHRS4, can have a *trans*-regulatory role in gene expression through histone modifications (100,101). LncRNAs can also serve as protein scaffolds for histone-modifying enzymes. For example, lncRNA AGAP2-AS1 acts as a protein scaffold and binds to the polycomb repressive complex 2 (PRC2) core catalytic subunit EZH2 and lysine-specific demethylase LSD1 to promote histone modifications in pancreatic adenocarcinoma (102), glioma (103), non-small cell lung cancer (104), and gastric cancer (105). Through this mechanism the expression of target genes is suppressed, and cancer progression is promoted. The lncRNA CDKN2B-AS1 can bind to both histone acetyltransferases CBP and SMYD3 to promote acetylation of lysine 27 on histone 3 (H3K27ac) and H3K4me3 at the NUF2 promoter, which further enhances NUF2 expression (34). Conversely, lncRNAs can act as a protein decoy to regulate histone modification. For example, LINC00261 binds to the acetylase P300/CBP complex, inhibiting its binding to the c-Myc gene promoter to reduce H3K27ac and inhibit pancreatic cancer progression by suppressing c-Myc expression (106). Similarly, lncRNA DLEU2 can also act as a protein decoy for EZH2 (107).

ATP-dependent chromatin remodeling. ATP-dependent chromatin remodeling complexes are divided into four major classes: SWI/SNF, ISWI, CHD, and INO80 (108). The complexes can alter the accessibility of transcription factors to DNA by disrupting the interaction between DNA and histones using the energy generated by ATP hydrolysis, altering the position of nucleosomes along the DNA or replacing histones (94,95). LncRNAs are also involved in this process. Subunits of the INO80 complex, INO80 and RUVBL2, bind to the lncRNA HAND2-AS1. This process activates BMPR1A expression and ultimately stimulates the self-renewal of hepatocellular carcinoma stem cells by recruiting INO80 to the BMPR1A promoter and forming the formation complex (109). Similarly, Tang *et al* reported that many lncRNAs in cancer interact with SWI/SNF and thus participate in the regulation of chromatin remodeling (110).

DNA methylation. In humans, DNA methylation occurs mainly at the cytosine 5' carbon atom of CpG dinucleotides. DNA methylation is catalyzed by the active DNA methyltransferases, DNMT1, DNMT3a, and DNMT3b that add methyl groups to cytosine to form 5-methylcytosine (5mC) (111,112). CpG dinucleotides usually exist in CpG islands in the promoter region of the human genome (113). Methylation of CpG islands can directly or indirectly inhibit the binding of transcription factors to promoters (114). LncRNAs can directly bind to these active DNA methylases and regulate gene expression, thereby interfering with cancer development (115-118). LncRNA LINC01270 is highly expressed in esophageal cancer and can act as a protein scaffold to simultaneously bind to DNMT1, DNMT3a, and DNMT3b. This mechanism mediates the hypermethylation of GSTP1 promoter, inhibiting its expression and promoting esophageal cancer progression and drug resistance (119). Interestingly, in colon cancer cells, lncRNA lnc-LALC can also recruit DNMT1, DNMT3a, and DNMT3b to the LZTS1 promoter simultaneously, but this requires direct binding of lnc-LALC to EZH2 (120). The lncRNA PARTICLE, which is highly expressed in response to low irradiation, promotes both DNA and histone methylation by binding to DNMT1 and the PRC2 core subunit SUZ12 and suppresses the expression of tumor suppressor MAT2A in cis as well as the tumor suppressor WWOX in *trans* (121,122).

DNA methylation is a stable modification process; however, ten-eleven translocation (TET) family proteins catalyze the conversion of 5mC to 5-hydroxymethylcytosine (5hmC), 5-formylcytosine (5fC), and 5-carboxycytosine (5caC). 5HmC is diluted during DNA replication, while 5fC and 5caC are removed by thymine DNA glycosylase (TDG), resulting in DNA demethylation (112,123). LncRNA TARID can bind to growth arrest and DNA damage-inducible 45A (GADD45A), a protein that mediates DNA demethylation. Through this interaction, TARID directs GADD45A cis to the tumor suppressor TCF21 promoter and indirectly recruits TETs as well as TDG, which can bind to GADD45A and co-mediate DNA demethylation (123). Similarly, lncRNA ZNF667-AS1 can bind to TET1 and histone H3K27 demethylase to promote both DNA and histone demethylation at the ZNF667 and E-calmodulin promoters, thereby inhibiting the development of esophageal squamous epithelial carcinoma (25).

5. Summary and prospects

Genomic instability is a feature of most cancers that undoubtedly contributes to cancer progression and heterogeneity through the accumulation of oncogenic and cancer suppressor genic mutations, regardless of whether it acts as a 'passenger' or a 'driver' in cancer. Although the exact mechanism is unknown, cancer cells have a tolerance limit to genomic instability, which indicates the potential of genomic destabilization as a therapeutic approach to cancer. Investigating the mechanisms of tolerance to genomic instability in cancer cells may provide new insights into cancer treatment. The aberrantly expressed lncRNAs in cancer cells and their binding proteins form networks that regulate genomic instability. Exploitation of lncRNA-RBP networks may provide new biological markers for cancer diagnosis and prognosis as well as new molecular targets and entry points for driving genomic instability to the limit of cellular tolerance or suppressing it in cancer therapies. However, the causal relationship between dysregulated lncRNA expression and genomic instability in many cancers has not yet been verified, and the exact molecular mechanism between the two remains unclear, which warrants further investigations.

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Authors' contributions

KY and KW conceived the study. KY drafted the manuscript. KY, KW and XL made substantial contributions to the interpretation, drafting the manuscript and revising it critically for important intellectual content. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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