Abstract. Long non-coding RNAs (lncRNAs) fulfill important roles in the majority of cellular processes. Previous studies have demonstrated that lncRNAs are involved in the pathogenesis of various diseases, including cancer. However, to date, the functions of only a small number of the known lncRNAs have been well-documented. lncRNAs comprise a class of multifunctional non-coding transcripts that are able to interact with different types of biomolecules. Interactions between lncRNAs and RNA-binding proteins (RBPs) provide an important mechanism through which lncRNAs exert their regulatory functions, mainly through findings on 'generalized RBPs'. Regulatory effects on lncRNAs mediated by RBPs have also been explored. Taking account of the research that has been completed to date, the continued and in-depth study of the bidirectional interactions between lncRNAs and RBPs will prove to be of major importance for understanding the pathogenesis of cancer and for developing effective therapies. The present review aims to explore the interactions between lncRNAs and RBPs that have been investigated in cancer, taking into consideration several different aspects, including the regulation of expression, subcellular localization and the mediation of diverse functions.

1. Introduction

Non-coding RNA (ncRNA) refers to RNAs that lack protein coding ability, which are ubiquitously expressed in human cells. Findings from two large-scale genome projects, FANTOM (1) and ENCODE (2), revealed that 80% of the human genome is transcriptionally active, whereas only 2% of the human genome encodes proteins. ncRNAs with a length of >200 nucleotides are known as long ncRNAs (lncRNAs) and participate in diverse biological processes (3). According to a previous study, the number of identified lncRNAs in humans is >60,000 (4).

lncRNAs were previously considered as non-functional ‘junk’ generated during the process of transcription; however, numerous studies published more recently have reported that lncRNAs fulfill important roles in biological processes. Studies published to date, however, have been rather preliminary and an understanding of the functions of lncRNAs in the cell, including in processes of reproduction, evolution, cognition and disease, remain in the infancy stages (5); therefore, only a limited number of lncRNAs have been annotated (6). For these reasons, great potential and value lies in performing research on lncRNAs and they have consequently become a ‘hotspot’ area in biological research. Several studies have explored the diverse and complex roles of lncRNAs in various biological processes. lncRNAs interact with biological molecules, such as mRNAs, DNA, proteins and microRNAs (miRNAs), thereby modulating epigenetic, transcriptional, post-transcriptional, translational and post-translational events of gene expression (7,8). Wang and Chang (9) summarized and classified the interactions that may occur between lncRNAs and these molecules into four archetypes, namely signal, decoy, guide and scaffold, and these archetypes may co-exist or overlap with each other.

At the molecular level, interactions between RNA and protein are important and common, as they fulfill key roles in cellular processes (10-14). RNA-binding proteins (RBPs) are a class of proteins that bind RNA through one or more RNA-binding domains (RBDs), which determines the fate or function of RNA. RBPs are involved in virtually all aspects of RNA metabolism through the formation of dynamic functional ribonucleoprotein (RNP) complexes with RNA (14,15). A regulatory role for RBPs with respect to RNA has been widely reported in previous studies on mRNA and miRNA (16-19).
However, more recent studies on IncRNAs have reported that numerous IncRNAs are implicated in the recruitment, organization, activation or inhibition of RBPs, indicating that RNA is also able to regulate RBPs (15,20,21). These results indicate that the regulatory interactions that occur between RBPs and RNA are bidirectional, particularly in the case of IncRNAs.

Numerous studies have examined the functions of RBPs, and therefore, knowledge on their scope and range of biological roles is constantly expanding. Previous studies reported that RBPs possess certain canonical RBDs, such as the RNA recognition motif, the KM domain and zinc finger motif, all of which are specifically recognized and bound by RNAs (10,15). This group of RBPs, which are referred to as ‘classical’ RBPs, has been extensively studied. However, proteomics studies have reported on the identification of certain non-classical RBPs that lack these canonical RBD domains; these non-canonical domains do not affect the binding of the RBPs to RNA (15,22,23). The mechanism of binding of non-classical RBPs to RNAs may involve multiple factors, including the molecular spatial structure, intracellular localization and expression level. On the other hand, DNA-binding proteins (DBPs), which are proteins that bind to DNA, have mainly been studied independently of RBPs owing to their different structural features. For instance, transcription factors are well established as a class of typical DBPs that recognize specific DNA sequences to regulate gene expression. However, emerging evidence has revealed that certain IncRNAs that are located in the nucleus are able to competitively bind to transcription factors through sites similar to DNA-binding motifs, thus preventing them from binding to their target DNA (24-26). This class of proteins with the dual function of binding both RNA and DNA are referred to as DNA- and RNA-binding proteins (DRBPs). The distinction between the concepts of DBP and RBP has become gradually blurred over time (20), and this blurring has mainly occurred where IncRNAs are involved. Therefore, the current review aimed to mainly explore ‘generalized RBPs’, which comprise all types of proteins or protein complexes that directly bind to and interact with RNA, including classical and non-classical RBPs, as well as certain unique RBPs or RBP complexes, such as transcription factors, protein kinases and chromatin-modified complexes.

Various studies have reported that IncRNAs are closely associated with cancer. IncRNAs are abnormally expressed in the majority of cancer types and have been indicated to exert regulatory roles in various cancer phenotypes through different molecular mechanisms (27-30). In addition, previously published studies have indicated that interactions between IncRNAs and RBPs provide the main mechanism through which IncRNAs exert their function (31-33). Other studies have indicated that interactions between IncRNAs and RBPs are involved in the occurrence and development of various types of disease, including cancer (34-38). Therefore, interactions between IncRNAs and RBPs have been suggested to fulfill key roles both in carcinogenesis and in the progression of cancer. The next chapter summarizes the common interactions that have been identified between IncRNAs and RBPs in cancer from the perspectives of molecular structure, expression level, subcellular localization and interactome. The topics covered in the text of the present review are summarized in Fig. 1 and Table I.

2. Regulation of RBPs by IncRNAs in cancer

Regulation of post-translational modification. Interactions between IncRNAs and RBPs alter the structure of RBPs and the most well-studied mechanism to date in the investigation of this phenomenon has been post-translational modification of RBP. Protein ubiquitination is widely involved in all life activities of cells and has an important role in protein degradation. A total of two major protein degradation pathways, i.e., the ubiquitin-proteasome pathway and the autophagy-lysosome pathway, are implicated in protein ubiquitination (39,40). Previous studies have demonstrated that cancer-associated IncRNAs are able to change the ubiquitination status of a protein after it binds to RBP (41-43). A study on hepatocellular carcinoma (HCC) reported that the binding of IncRNA-Low Expression in Tumor (IncRNA-LET) promoted the ubiquitination and degradation of protein nuclear factor 90 (NF-90) (41). RNA immunoprecipitation (RIP) experiments using antibodies raised against important E3 ligases (such as phr2, wwp2 and skp2) in liver cancer in previous studies were performed in this study; however, IncRNA-LET was not detected. These results indicated that IncRNA-LET may have combined with other unknown E3 ligases or may have changed the conformation of NF-90, resulting in exposure of ubiquitination sites, thereby increasing the ubiquitination level of NF-90. Another study reported that IncRNA overexpressed in colon carcinoma-1 (OCC-1) binds to classical RBP human antigen R (HuR) in colorectal cancer (CRC). The study revealed that OCC-1 is able to upregulate ubiquitination of HuR and decrease its expression level through promoting the binding of HuR to the E3 ubiquitin ligase β-Trcp1, thus inhibiting the stabilization of HuR on its target mRNAs (42). Xue et al (43) explored the specific binding of HOX antisense intergenic RNA (HOTAIR) to Runt-related transcription factor 3 (RUNX3) protein through bioinformatic analysis combined with pull-down, RIP and truncation experiments. Mechanistic studies demonstrated that HOTAIR promoted the binding of RUNX3 to the E3 ligase Mxi3b and accelerated degradation of RUNX3 through the ubiquitin-proteasome pathway, thereby improving the invasive ability of gastric cancer cells. These results suggested that IncRNAs are able to mediate and promote interactions between RBPs and E3 ligase, increasing the protein ubiquitination level and downregulating the expression of key regulatory proteins in cancer.

Conversely, other interactions that have been identified between IncRNAs and RBPs have been indicated to lead to inhibition of the ubiquitination level of certain cancer-associated proteins. For instance, IncRNA terminal differentiation-induced non-coding RNA (TINCR), which is highly expressed in nasopharyngeal carcinoma (NPC), was indicated to reduce the ubiquitination level after binding to ATP citrate lyase (ACLY) protein (44). Silencing TINCR led to an increase in the ubiquitination level of ACLY. Of note, the proteasome inhibitor MG132 was observed to reverse this effect, implying that the stabilizing effect of TINCR on ACLY is achieved through inhibiting the ubiquitin-proteasome pathway, and an elevated expression of ACLY promoted
both the progression and the chemotherapeutic resistance of NPC (44). In a separate study by Wang et al (45), long intergenic ncRNA for insulin-like growth factor 2 mRNA-binding protein 2 (IGF2BP2) Stability (LINRIS) was indicated to be highly expressed in CRC and to be associated with poor prognosis. They reported that the protein IGF2BP2 is able to stabilize its downstream target, c-Myc mRNA, which is the core regulator of aerobic glycolysis in CRC. LINRIS interacts with IGF2BP2, thereby leading to a decrease in its ubiquitination level. However, this function of LINRIS was not indicated to be mediated via the proteasome pathway, but through the autophagy-lysosomal pathway, which led to a higher expression level of IGF2BP2, promoting the aerobic glycolysis of CRC cells. Of note, the intrinsic molecular mechanism involved the binding of LINRIS to block the IGF2BP2 ubiquitin site, Lys139. Therefore, there is accumulating evidence that the physical binding of IncRNAs may lead to inhibition of protein ubiquitination via the shielding of ubiquitination sites, thereby maintaining the stability of key proteins in cancer.

Another common mode of protein modification to be considered in terms of interactions that occur between IncRNAs and RBPs is phosphorylation. IncRNAs are able to inhibit phosphorylation of their binding partner RBP through a mechanism similar to that employed in ubiquitination inhibition. For instance, the IncRNA NF-κB interacting IncRNA binds to NF-κB/IκB complex and inhibits the phosphorylation of IκB via IκB kinase by 'masking' the phosphorylation sites of IκB, thereby reducing degradation of IκB and maintaining the inhibition of IκB on NF-κB, ultimately suppressing breast cancer (BRC) metastasis (46). Several studies have demonstrated how the facilitating effect of IncRNAs on RBP phosphorylation is a common occurrence. Pyruvate kinase M2 (PKM2), an isoenzyme of pyruvate kinase, is a key enzyme in glycolysis. PKM2 promotes tumor growth by regulating the expression of genes involved in cell proliferation, migration and apoptosis. The IncRNA highly upregulated in liver cancer (HULC) was indicated to directly bind to PKM2 and promote its phosphorylation, thereby inhibiting the formation of the tetramer conformation (which is its activated state), ultimately downregulating its activity (47). As another example, polo-like kinase 1 (PLK1) is a key regulator of the cell cycle and DNA damage repair. Aurora A/PLK1-associated IncRNA binds to PLK1 and promotes the phosphorylation and activation of PLK1, thereby inhibiting the apoptosis of tumor cells (48). The IncRNA-induced phosphorylation of RBP may cooperate with ubiquitination to promote protein degradation (49,50). For instance, enhancer of Zeste homolog 2 (EZH2) is a component of polycomb suppress complex 2, which exerts important roles in the occurrence and metastasis of CRC, among other cancer types. Cyclin-dependent kinase 1 (CDK1) is able to induce
### Table I. Interaction between lncRNAs and RBPs in cancer.

#### A. lncRNAs regulate post-translational modification of RBPs

| lncRNA  | Interacting RBP | Interaction mechanisms | Resulting effects on cancer (Refs.) |
|---------|----------------|------------------------|-------------------------------------|
| LET     | NF-90          | Downregulates NF90 protein abundance via the ubiquitin-proteasome pathway | Represses the invasion of HCC (41) |
| OCC-1   | HuR            | Enhances binding of ubiquitin E3 ligase β-TrCP1 to HuR | Suppresses cell growth in CRC (42) |
| HOTAIR  | RUNX3          | Enhances binding of E3 ligase Mex3b to RUNX3 | Enhances the invasion of GC (43) |
| TINCR   | ACLY           | Protects ACLY from ubiquitination | Promotes proliferation, metastasis and cisplatin resistance of NPC (44) |
| LINRIS  | IGF2BP2        | Blocks IGF2BP2 ubiquitin site K139 and downregulates its ubiquitination level | Promotes the aerobic glycolysis in CRC (45) |
| NKILA   | NF-κB/κB complex | Inhibits phosphorylation by masking the phosphorylation sites of κB | Suppresses the metastasis of BRC (46) |
| HULC    | PKM2           | Promotes phosphorylation of PKM2 and inhibits its tetramer formation | Promotes aerobic glycolysis of HCC cells (47) |
| APAL    | PLK1           | Promotes phosphorylation and activation of PLK1 | Maintains the survival of BRC, NSCLC cells (48) |
| ANCR    | EZH2           | Promotes phosphorylation of EZH2 and facilitates its ubiquitination | Inhibits the invasion and metastasis of BRC (51) |
| RMST    | FUS            | Promotes SUMOylation of FUS and inhibits its ubiquitination | Suppresses GBM cell mitophagy (54) |
| pSTAR   | hnRNP K        | Inhibits deSUMOylation of hnRNP K and promotes formation of p53-hnRNP K complex | Inhibits HCC cell growth through inducing cell cycle arrest (55) |

#### B. lncRNAs regulate intracellular localization of RBPs

| lncRNA  | Interacting RBP | Interaction mechanisms | Resulting effects on cancer (Refs.) |
|---------|----------------|------------------------|-------------------------------------|
| BLACAT2 | WDR5           | Recruits WDR5 to the promoter region of VEGF-C gene | Promotes lymphangiogenesis and lymphatic metastasis in BLC (56) |
| LNMAT1  | hnRNP L        | Recruits hnRNP L to the promoter region of CCL2 | Promotes lymphatic metastasis of BLC (57) |
| HOXA11-AS | WDR5     | Recruits WDR5 to the promoter region and increases expression of β-catenin | Promotes cell cycle progression and metastasis in GC (58) |
| HOXA11-AS | EZH2      | Recruits EZH2 to the promoter region and inhibits the transcriptional level of P21 | Promotes cell cycle progression and metastasis in GC (58) |
| AC020978 | PKM2        | Promote PKM2 to translocate from nucleus to cytoplasm | Promotes proliferation and glycolytic metabolism of NSCLC (59) |
| XIST    | SMAD2         | Inhibits transport of SMAD2 into the nucleus | Promotes cell growth and DDP chemoresistance in NSCLC (60) |
| GAS5    | YAP           | Blocks translocation of YAP from the cytoplasm into nucleus | Inhibits proliferation, invasion and metastasis in CRC (61) |
### Table I. Continued.

#### B, lncRNAs regulate intracellular localization of RBPs

| lncRNA       | Interacting RBP | Interaction mechanisms                                                                 | Resulting effects on cancer                                      | (Refs.) |
|--------------|-----------------|----------------------------------------------------------------------------------------|------------------------------------------------------------------|--------|
| OLA1P2       | STAT3           | Inhibits formation of phosphorylated STAT3 and restricts its transport into nucleus     | Inhibits proliferation, invasion and metastasis in CRC           | (62)   |
| EPB41L4A-AS1 | HDAC2           | Restricts release of HDAC2 from nucleolus to nucleoplasm                                | Inhibits glycolysis and glutaminolysis in CC and HCC cells       | (63)   |

#### C, lncRNAs affect interaction network of RBPs

| lncRNA       | Interacting RBP | Interaction mechanisms                                                                 | Resulting effects on cancer                                      | (Refs.) |
|--------------|-----------------|----------------------------------------------------------------------------------------|------------------------------------------------------------------|--------|
| FGF13-AS1    | IGF2BP          | Inhibits stabilizing role of IGF2BPs on c-Myc mRNA                                      | Inhibits glycolysis and stemness of BRC                         | (64)   |
| LINC01093    | IGF2BP1         | Facilitates GL11 mRNA degradation by blocking the binding of IGF2BP1                   | Inhibits proliferation and metastasis of HCC                    | (65)   |
| FILNC1       | AUF1            | Downregulates c-Myc expression by inhibiting interaction of AUF1 with c-Myc mRNA       | Represses energy metabolism and inhibits RC development          | (66)   |
| MALAT1       | SFPQ            | Releases PTBP2 from the SFPQ/PTBP2 complex                                             | Promotes tumor growth and metastasis in CRC                     | (67)   |
| P53RRA       | G3BP1           | Displaces p53 from the G3BP1 complex                                                   | Promotes ferroptosis and apoptosis of LC cells                  | (68)   |
| MYCLO-1      | HuR             | Inhibits binding of HuR to CDKN1A                                                      | Promotes the proliferation of CRC cells                         | (69)   |
| MYCLO-2      | hnRNP K         | Inhibits binding of hnRNP K to CDKN2B                                                  | Promotes the proliferation of CRC cells                         | (69)   |
| LUCAT1       | NCL             | Inhibits binding of NCL to G4 sequence in the MYC promoter region                      | Promotes the proliferation of CRC cells                         | (70)   |
| THOR         | IGF2BP          | Stabilizes downstream target mRNAs of IGF2BP                                           | Facilitates proliferation in LC and melanoma cells               | (71)   |
| AFAP1-AS1    | AUF1            | Promotes binding of AUF1 to HER-2 mRNA under exosome mediation                         | Promotes trastuzumab resistance in BRC                         | (72)   |
| HOXA11-AS    | STAU1           | Promotes binding of STAU1 to KLF2 mRNA and accelerates degradation of KLF2 mRNA       | Promotes cell cycle progression and metastasis in GC           | (58)   |
| RP11         | hnRNPA2B1       | Promotes binding of hnRNPA2B1 to Siah1 and Fbxo45 mRNAs and accelerates their degradation | Promotes migration, invasion, EMT and liver metastasis in CRC | (73)   |
| SCHLAP1      | hnRNP L         | Stabilizes ACTN4 by promoting interaction between hnRNP L and ACTN4                    | Promotes growth of GBM cells                                    | (74)   |
| ZFAS1        | NOP58           | Activates NOP58 to promote recruitment of SNORD12C and SNORD78                         | Promotes proliferation and inhibits apoptosis in CRC             | (75)   |
| PiHL         | GRWD1           | Promotes binding of GRWD1 to RPL11 and isolates RPL11 from MDM2                       | Maintains cell proliferation and induces 5-FU chemoresistance in CRC | (76)   |
| LINCO0051    | EZH2            | Enhances the enrichment of EZH2 on IL-24 promoter and silences IL-24 expression        | Promotes proliferation and inhibits apoptosis of CRC cells       | (78)   |
### Table I. Continued.

#### C. lncRNAs affect interaction network of RBPs

| lncRNA | Interacting RBP | Interaction mechanisms | Resulting effects on cancer | (Refs.) |
|--------|-----------------|------------------------|-----------------------------|---------|
| CYTOR  | NCL, Sam68      | Scaffolds the trimer NCL/CYTOR/Sam68 | Promotes proliferation, migration, invasion, EMT and metastasis in CRC | (79)    |
| HITTERS | MRE11-RAD50-NBS1 protein complex | Facilitates formation of MRN protein complex as an RNA scaffold | Promotes the invasion and lung metastasis of OSCC | (80)    |
| HOTAIR | HBXIP, LSD1      | Forms an RNA/protein complex to recruit LSD1 to the promoters of c-Myc target genes | Promotes the proliferation of BRC cells | (81)    |
| LBCS   | hnRNP K, EZH2    | Forms a complex mediating H3K27me3 in the SOX2 promoter region | Inhibits self-renewal and chemoresistance of BLC stem cells | (82)    |

#### D. RBPs regulate lncRNA expression at post-transcriptional level

| lncRNA | Interacting RBP | Interaction mechanisms | Resulting effects on cancer | (Refs.) |
|--------|-----------------|------------------------|-----------------------------|---------|
| NEAT1  | SRSF1           | Maintains the stability of NEAT1 | Facilitates GBM cell proliferation and cell cycle progression | (87)    |
| NEAT1_1| HuR             | Maintains the stability of NEAT1_1 | Promotes OC cell proliferation and invasion | (88)    |
| lncRNA-P21 | HuR             | Accelerates lincRNA-p21 degradation by recruiting let-7/RISC | Facilitates JunB and β-catenin translation and increases the levels of these proteins in HeLa cells | (92)    |
| HOTAIR | HuR             | Accelerates HOTAIR degradation via let7/Ago2 pathway | Inhibits the ubiquitination of Ataxin-1 and Snurportin-1 and decelerates their degradation in HeLa cells | (93)    |
| NEAT1, TUG1 | PABPN1         | Accelerates NEAT1 and TUG1 degradation via RNA exosome complexes | Promotes the degradation of PABPN1-sensitive lncRNAs in HeLa cells | (96)    |
| HULC   | IGF2BP1         | Accelerates HULC degradation by recruiting CCR4-NOT complex | Reduces the expression of HULC in HCC cells | (98)    |

#### E. RBPs regulate lncRNAs localization and transport

| lncRNA | Interacting RBP | Interaction mechanisms | Resulting effects on cancer | (Refs.) |
|--------|-----------------|------------------------|-----------------------------|---------|
| MALAT1 | HuR/MTCH2       | Facilitates MALAT1 to shuttle into mitochondria | Promotes the proliferation, migration and invasion of HCC | (101)   |
| RMRP   | HuR             | Facilitates RMRP nuclear export | Enhances oxygen consumption rates and mitochondrial DNA replication priming in HeLa cells | (105)   |
| RMRP   | GRSF1           | Facilitates RMRP accumulation in mitochondria | Enhances oxygen consumption rates and mitochondrial DNA replication priming in HeLa cells | (105)   |
Table I. Continued.

### E, RBPs regulate lncRNAs localization and transport

| lncRNA   | Interacting RBP | Interaction mechanisms                                                                 | Resulting effects on cancer (Refs.) |
|----------|-----------------|----------------------------------------------------------------------------------------|-------------------------------------|
| MALAT1   | SNRNP70         | Facilitates nuclear and genome-wide localization of MALAT1                              | Maintains the localization of both nascent and polyadenylated lncRNA transcripts to chromatin in HeLa cells (106) |
| LNMAT2   | hnRNPA2B1       | Facilitates LNMAT2 loading into exosomes and secreting out of cell                      | Promotes lymphatic metastasis in BLC (109) |

### F, RBPs mediate lncRNA function

| lncRNA   | Interacting RBP | Interaction mechanisms                                                                 | Resulting effects on cancer (Refs.) |
|----------|-----------------|----------------------------------------------------------------------------------------|-------------------------------------|
| MALAT1   | SRSF1           | Mediates the interaction between MALAT1 and mutant p53 or ID4                           | Promotes angiogenesis through repression of VEGFA_{16b} in BRC (110) |
| PURPL    | HuR             | Mediates the interaction between PURPL and MYBBP1A                                     | Promotes tumor growth in CRC (111)  |

LET, low expression in tumor; NF-90, nuclear factor 90; HCC, hepatocellular carcinoma; OCC-1, overexpressed in colon carcinoma-1; HuR, human antigen R; CRC, colorectal cancer; HOTAIR, HOX antisense intergenic RNA; RUNX3, Runt-related transcription factor 3; GC, gastric cancer; TINC, terminal differentiation-induced non-coding RNA; ACLY, ATP citrate lyase; NPC, nasopharyngeal carcinoma; LINRIS, long intergenic noncoding RNA for IGF2BP2 stability; IGF2BP, insulin-like growth factor 2 mRNA-binding protein; NKILA, NF-xB interacting lncRNA; NF-xB, nuclear factor-xB; IxB, inhibitor of NF-xB; BRC, breast cancer; HULC, highly upregulated in liver cancer; PKM2, pyruvate kinase M2; APAL, Aurora A/PLK1-associated lncRNA; PLK1, Polo-like-kinase 1; NSCLC, non-small cell lung cancer; ANCR, anti-differentiation ncRNA; EZH2, enhancer of zeste homolog 2; RMST, rhabdomyosarcoma 2 associated transcript; FUS, fused in sarcoma; GBM, glioblastoma; SUMO, small ubiquitin-like modifier; pSTAR, p53-stabilizing and activating RNA; hnRNP, heterogeneous nuclear ribonucleoprotein; BLACAT2, bladder cancer-associated transcript 2; WDR5, WD repeat containing protein 5; BLC, bladder cancer; LNMAT1, lymph node metastasis associated transcript 1; XIST, X inactive-specific transcript; SMAD2, mothers against decapentaplegic protein 2; YAP, yes-associated protein; STAT3, signal transducer and activator of transcription 3; HDAC2, histone deacetylase 2; CC, cervical cancer; FGF13, fibroblast growth factor 13; GLI1, glioma-associated oncogene homolog 1; FILNC1, FoxO-induced long non-coding RNA 1; AUF1, ARE/poly(U)-binding/degradation factor 1; RC, renal cancer; MALAT1, metastasis associated with lung adenocarcinoma transcript-1; PTBP2/PTB, polyynimyosin-tract-binding protein; SFPQ/PSF, PTB-associated splicing factor; G3BP1, Ras GTPase-activating protein-binding protein 1; LC, lung cancer; CDKN, cyclin-dependent kinase inhibitor; LUCAT1, lung cancer associated transcript 1; NCL, nucleolin; G4, G-quadruplex; THOR, testis-associated highly-conserved oncogenic long non-coding RNA; AFAP1-AS1, actin filament associated protein 1 antisense RNA 1; STAU1, staufen1; KLF2, Kruppel-like factor 2; Sia1, seven in absentia homolog 1; Fbxo45, F-box only protein 45; EMT, epithelial mesenchymal transition; SChLAP1, SWI/SNF complex antagonist associated with prostate cancer 1; ACTN4, alpha-actinin-4; ZFAS1, zinc finger NFX1-type containing 1 antisense RNA 1; NOP58, nucleolar protein 58; PHL, P53 inhibiting lncRNA; GRWD1, glutamate-rich WD repeat-containing protein 1; RL11, ribosomal protein L11; MDM2, murine double minute 2 protein; CYTOR, cytoskeleton regulator; HITTERS, HERPUD1 intronic transcript of ER stress; MRE11, meiotic recombination 11 homolog 1; RAD50, DNA repair protein 50; NBS1, Nijmegen breakage syndrome protein 1; OSCC, oral squamous cell carcinoma; HBXIP, hepatitis B X-interacting protein; LSD1, lysine-specific demethylase 1; LBCS, low expressed in bladder cancer stem cells; SRSF1, serine/arginine rich splicing factor 1; NEAT1, nuclear-enriched abundant transcript 1; OC, ovarian cancer; RISC, RNA-induced silencing complex; PABPN1, poly(A)-binding protein nuclear 1; TUG1, taurine upregulated gene 1; MTCH2, mitochondrial carrier homolog 2; GRSF1, G-rich RNA sequence binding protein; RMRP, RNA component of mitochondrial RNA-processing endonuclease; snRNP, small nuclear ribonucleoprotein; ID4, inhibitor of differentiation 4; VEGFA, vascular endothelial growth factor A; PURPL, p53 upregulated regulator of p53 levels; MYBBP1A, MYB binding protein 1A.
the phosphorylation of EZH2 at the Thr345 and Thr487 phosphorylation sites, thereby promoting degradation of EZH2 through the ubiquitin-proteasome pathway. Furthermore, the lncRNA anti-differentiation nccRNA directly binds to EZH2. The complex that arises promotes further interaction between CDK1 and EZH2, leading to a heightened increase in the level of phosphorylation of EZH2 at the Thr345 and Thr487 sites (51).

Small ubiquitin-like modifier (SUMO) is a ubiquitin-like protein that is able to modify target proteins through a process known as SUMOylation, which operates via a mechanism similar to that of ubiquitination. However, SUMOylation is different from ubiquitination, in that it does not promote degradation of its target protein. SUMOylation fulfills an important role in maintaining chromosomal integrity and regulatng cell proliferation. Previous studies have reported that SUMOylation exerts a key role in cancer progression (52,53), and lncRNAs are involved in the regulation of cancer through modulating SUMOylation of their binding partner RBPs. Rhabdomyosarcoma 2 associated transcript (RMST) is a highly expressed lncRNA in glioblastoma (GBM), and RNA pull-down and RIP experiments have indicated that it directly binds to fused in sarcoma (FUS) protein. The interaction between RMST and FUS promotes SUMOylation of FUS at the Lys333 site, thereby inhibiting ubiquitination and upregulating the expression of FUS, which ultimately leads to inhibition of the autophagy of GBM cells mediated via downstream targets (54). Similar findings were reported by Qin et al (55) in HCC cells, i.e., that binding of the lncRNA p53-stabilizing and activating RNA inhibited the deSUMOylation of RBP heterogeneous nuclear RNP K (hnRNP K), thereby promoting the formation of the p53-hnRNP K complex. Increased binding of hnRNP K to p53 inhibited murine double minute 2 protein (MDM2)-dependent p53 ubiquitination and degradation, thereby increasing p53 stability and ultimately leading to inhibition of the proliferation of HCC cells.

Considering all of the above together, these studies have indicated that interactions between lncRNAs and their partner RBPs in different types of cancer modulate post-translational modifications of RBPs either by shielding modification sites or through linking modification enzymes. Changes in RBP structure following the modification led to changes in the expression level of the given RBP and this is influenced by the synergistic mechanism of ubiquitination and other protein modifications.

Regulation of intracellular localization. Protein function is closely associated with the localization of the protein of concern in the cells, and the binding of a lncRNA may lead to a change in the intracellular distribution of RBPs. A common regulatory mechanism of gene expression in cancer involves the localization of transcription factors or transcriptional co-regulators by nuclear-localized lncRNAs precisely to the promoter region of target genes. Bladder cancer (BLC)-associated transcript 2 is an lncRNA that is highly expressed in BLC and which recruits WD repeat-containing protein 5 (WDR5) to the promoter region through their direct interaction, resulting in H3K4 trimethylation of the vascular endothelial growth factor C (VEGF-C) gene. These changes promote both VEGF-C expression and lymphangiogenesis and lymphatic metastasis of BLC (56). In addition, lymph node metastasis-associated transcript 1 (LNMAT1) has been indicated to bind to hnRNP L, recruiting it to the promoter region of chemokine C-C motif ligand 2 (CCL2), which causes an increase in the occupation rate of hnRNP L and H3K4 trimethylation of the promoter region of CCL2, thereby promoting lymphatic metastasis of BLCC (57). In gastric cancer, the antisense (AS) lncRNA-HOXA11-AS recruits WDR5 to the promoter region and increases the expression of β-catenin via binding to WDR5. Furthermore, HOXA11-AS has been demonstrated to recruit EZH2 to the promoter region of P21, where it causes an inhibition of the transcription of P21 (58). Collectively, these results suggest that lncRNAs are implicated in the localization of RBPs on the promoter regions of their target genes, where they elicit either positive or negative regulation of transcription of the genes concerned.

The roles of lncRNAs in nucleocytoplasmic localization of the RBPs that they bind are diverse. For instance, lncRNA-AC020978 is upregulated in non-small cell lung cancer (NSCLC) and its upregulation is strongly correlated with TNM staging and the clinical prognosis of NSCLC. AC020978 is also able to promote the translocation of PKM2 from the nucleus to the cytoplasm through their direct interaction, thereby promoting the activation of hypoxia-inducible factor-1α transcription during glucose starvation and hypoxia (59). In addition, the lncRNA X inactive-specific transcript was indicated to inhibit transport of the TGF-β effector factor SMAD2 into the nucleus through their direct binding, leading to transcriptional inhibition of both p53 and NLR family pyrin domain containing 3, which are key regulators of apoptosis and pyrolysis, ultimately leading to the facilitation of tumor growth in NSCLC and the promotion of cisplatin resistance (60). As a further example, dysregulation of the Hippo/Yes-associated protein (YAP) signaling pathway promotes tumorigenesis of CRC and other cancers, with YAP being a key factor in the Hippo signaling pathway. A previous study reported that growth arrest-specific 5 is able to block translocation of YAP from the cytoplasm into the nucleus through its binding to YAP, resulting in an accumulation of YAP in the cytoplasm, thereby promoting the ubiquitination degradation of YAP (61). Aspirin-induced lncRNA-OLA1P2 was reported to inhibit the formation of the phosphorylated STAT3 homodimer by binding to Tyr705 and restricting its entry into the nucleus, thus inhibiting metastasis of CRC (62). A study by Liao et al (63) reported that the regulation mediated by lncRNAs on RB localization occurs in a very precise manner. lncRNA-EPB41L4A-AS1 is regulated by p53, which is expressed at only a low level or is even deleted in a variety of human cancer types, a phenomenon that is associated with poor prognosis. EPB41L4A-AS1 is able to bind to histone deacetylase 2 (HDAC2) and co-localize with HDAC2 in the nucleolus. HDAC2 is subsequently released from the nucleolus into the nucleoplasm after silencing of EPB41L4A-AS1. In addition, an increased level of HDAC2 in the nucleoplasm enhances its binding on the promoter regions of the Von Hippel-Lindau and voltage-dependent anion channel 1 genes, which ultimately accelerates the processes of glycolysis and glutamine metabolism. These findings indicate that the roles of lncRNAs in terms of intracellular localization of RBP are
not limited to intracellular and extracellular distribution but also involve intranuclear localization.

Taken together, it has been amply demonstrated that the binding of lncRNAs to certain partner RBPs leads to significant changes in their expression and function through regulating their intracellular distribution, thus regulating the pathological processes of RBP-associated cancers.

**Effects on the RBP interaction network**

*General.* In addition to RNAs, RBPs are able to bind to several other types of biological molecules, including proteins and DNA. Studies have reported that binding of lncRNAs also affects the interaction network of RBPs and this mode of regulation is implicated in various human diseases, including cancer (58,64-82). Common ways in which lncRNAs regulate RBP-interaction networks in cancer are summarized below.

**Negative regulation.** The binding of lncRNAs has been indicated to suppress interactions between RBPs and other biomolecules through a mechanism similar to that employed by competing endogenous RNA, which is known as 'decoy' or 'competitive combination'. Competitive binding of lncRNAs is a common mechanism in cancer that leads to inhibition of the interactions between RBPs and their downstream cancer-associated mRNAs, proteins, DNA and other targets.

The inhibitory effects mediated by lncRNAs on the interactions between RBPs and mRNA frequently lead to increased degradation of the target mRNA, resulting in decreased expression at the post-transcriptional level. For instance, the lncRNA fibroblast growth factor 13-AS1 binds IGF2BP1, affecting their stabilizing role on c-Myc mRNA and reducing the expression level of c-Myc, thereby inhibiting glycolysis and the stemness of BRC cells (64). A new liver-specific lncRNA, LINC01093, was reported to competitively combine with IGF2BP1 and block its binding to glioma-associated oncogene homolog 1 (GLI1) mRNA, resulting in GLI1 mRNA degradation and leading to the suppression of proliferation and metastasis of HCC (65). It is noteworthy that certain stimulating factors are able to induce activation of this mechanism. For instance, FoxO-induced long non-coding RNA 1 causes downregulation of the expression of c-Myc protein under low-energy conditions via modulating the interaction of ARE/poly(U)-binding/degradation factor 1 (AUFI) with c-Myc mRNA through their direct competitive combination. Subsequently, c-Myc-mediated energy metabolism is inhibited following a decrease in c-Myc protein expression, leading to apoptosis and inhibition of the proliferation of renal cancer cells (66).

Competitive binding of lncRNAs may result in an inability of RBPs to form activated complexes with other proteins, producing a ‘sequestration’ effect that effectively suppresses the function of target proteins at the post-translational level. RBP polypyrimidine-tract-binding protein (PTBP2) has been implicated in promoting the growth of ovarian cancer and other tumors, and SFPQ protein, also known as PTB-associated splicing factor, is able to bind to PTBP2 and inhibit its function. Metastasis associated with lung adenocarcinoma transcript-1 (MALAT1) has been indicated to competitively bind to SFPQ and to release PTBP2 from the SFPQ/PTBP2 complex, thereby increasing tumor growth and metastasis (67). Similarly, binding of lncRNA p53RRA to Ras GTPase-activating protein-binding protein 1 (G3BP1) is able to displace p53 from the G3BP1 complex, leading to retention of p53 in the nucleus and consequently promoting cell cycle arrest, apoptosis and ferroptosis (68).

Furthermore, lncRNA binding is able to inhibit the DNA-binding ability of certain DRBPs, leading to inhibition of the expression of target genes at the transcriptional level. Cyclin-dependent kinase inhibitor 1A (CDKN1A) and CDKN2B are key target genes for the transcription factor MYC in mediating tumorigenesis. Kim et al (69) reported that a group of lncRNAs termed ‘MYCLO’ are induced by MYC, where MYCLO-1 and MYCLO-2 inhibit binding of the RBPs HuR and hnRNPK to the promoters of CDKN1A and CDKN2B, respectively. These inhibitory effects result in dysregulation of CDKN1A and CDKN2B expression and promote the proliferation of CRC. In addition, G-quadruplex (G4) is a negative regulator of transcription and a study performed on CRC by Wu et al (70) revealed that the lncRNA lung cancer associated transcript 1 is able to bind to nucleolin (NCL) through its G4 formation sequence, thereby inhibiting the binding of NCL to the G4 sequence in the MYC promoter region. This competitive binding leads to upregulation in the expression of MYC and further promotes the proliferation of CRC cells.

These findings collectively indicate that the binding of lncRNAs results in significant negative effects on the interactions between RBPs and other biomolecules and these are implicated in different stages of cancer progression.

**Positive regulation.** Activation of RBP function may require the participation of lncRNAs. In addition to the competitive inhibition mechanism, direct combination of lncRNAs may either guide or activate RBPs to function with other biomolecules. This type of positive regulation of lncRNAs occurs commonly in various types of cancer and results in an increase in the complexity of the RBP-interaction network.

Facilitating the interactions of RBPs with their downstream target mRNAs may be the most common mechanism through which lncRNAs activate RBP function by binding to RBPs without altering their expression levels. RBPs activated by lncRNAs in turn regulate the expression of certain cancer-associated genes by changing the stability of mRNA after direct binding has occurred, and they therefore participate in regulating the pathological processes of various types of cancer. Hosono et al (71) characterized the highly conserved oncogenic lncRNA Testis-associated highly-conserved oncogenic long non-coding RNA (THOR), which, although mainly expressed in normal tissue of the testis, is highly expressed in various types of cancer. Binding of THOR to IGF2BP promotes the stabilization of a series of related target mRNAs. Of note, the same effects of lncRNAs may be transmitted through exosomes. Han et al (72) reported that in BRC, lncRNA actin filament-associated protein 1 antisense RNA 1 (AFAP1-AS1), secreted by trastuzumab-resistant cells, becomes packed into exosomes. AFAP1-AS1, when combined with the RBP AUFI under exosomal mediation, promotes the binding of AUFI to HER-2 mRNA, thereby activating its translation without affecting the expression level, with a consequent increase in the expression of HER-2 protein promoting both trastuzumab resistance and metastasis of the BRC cells. Furthermore,
Interactions between lncRNAs and RBPs may lead to a reduction in the stability of target mRNAs bound to RBPs. For instance, in gastric cancer, lncRNA HOXA11-AS was indicated to induce degradation of Kruppel-like factor 2 (KLF2) mRNA through interacting with staufen-1, thereby downregulating the protein expression of KLF2 and promoting tumor proliferation and metastasis (58). Furthermore, the lncRNA RP11 was demonstrated to exhibit similar activity. High expression levels of RP11 are significantly positively correlated with the metastasis of CRC and this has been implicated in promoting the post-transcriptional expression of Zinc finger E-box containing homeobox 1 (Zeb1) protein. After their direct combination, RP11 promotes binding of hnRNPA2B1 to E3 ligase seven in absentia homolog 1 (Zeb1) protein, thereby accelerating their degradation, a process that inhibits degradation of Zeb1 through the proteasomal pathway that is associated with the two ligases (73).

Similarly, lncRNA is able to bind to RBP and facilitate its interactions with other proteins or protein complexes. For instance, in glioblastoma, the lncRNA SWI/SNF complex antagonist associated with prostate cancer 1 has an important role as a binding-protein partner of hnRNP L, promoting its interaction with α-actinin-4 (ACTN4). hnRNP L binds and stabilizes ACTN4 by blocking the ubiquitin-proteasome pathway, thereby activating the NF-kB signaling pathway, which accelerates the rate of cancer progression (74). In a recent study, Wu et al (75) reported on a novel mechanism that linked the lncRNA zinc finger NFX1-type containing 1 antisense RNA 1 (ZFAS1) with CRC progression. ZFAS1 is able to bind directly with nucleolar protein 58 (NOP58), the core component of small nucleolar ribonucleoprotein complex (SNORNP); upon activation of NOP58, this promotes the recruitment of the other proteins that are involved in the complexes SNORD12C and SNORD78, and further promotes the assembly of the three components to form SNORNP. Upregulated SNORNP promotes 2'-O methylation of 28S rRNA, leading to a high expression level of downstream target genes such as EIF4A3 and LAMC2, resulting in inhibition of the proliferation and invasion of CRC cells. Similarly, glutamate-rich WD repeat-containing protein 1 (GRWD1) has been reported to bind to p53 inhibiting lncRNA (PIHL) and ribosomal protein L11 (RPL11) in CRC (76). Of particular interest is that PIHL promotes binding of GRWD1 to RPL11, thereby isolating RPL11 from MDM2, followed by enhanced p53 ubiquitination, ultimately leading to rapid cell proliferation and chemotherapeutic resistance in CRC (76).

Of note, RBPs without direct DNA-binding ability are able to interact with DNA through the modulating effects of lncRNAs. Co-participation of the lncRNA lincRNA-p21 and hnRNPK is involved in the p53 (a classical tumor suppressor gene) signaling pathway. The lincRNA-p21-hnRNPK complex mediates binding of hnRNPK to the promoter region of p53 target gene, thereby suppressing the expression of its target genes (77). Lu et al (78) reported that the upregulation of LINC0051 promoted the progression of CRC, accompanied by downregulation of the expression of IL-24. LINC0051 combines with EZH2 and their interaction activates the silencing effect of EZH2 on IL-24 expression via enhancing its enrichment on the IL-24 promoter region. It is important to note that, in all the above cases, this RBP activation function of the lncRNA is always accompanied by its localization to the target gene promoter region of its partner RBP mediated by lncRNA.

In addition, lncRNAs are able to bind to multiple RBPs at the same time as a scaffold or platform, whereby the functions of the different RBPs are integrated, thus activating the protein complexes and promoting their functions of regulating gene expression. For instance, formation of the trimer NCL/CYTOR/Sam68 in CRC leads to acceleration of tumor cell epithelial-to-mesenchymal transition (EMT) and tumor progression via activating the NF-kB signaling pathway. Furthermore, the lncRNA cytoskeleton regulator has been indicated to activate the interaction between two RBPs, namely NCL and Sam68, as a scaffold in the trimer (79). A study by Wu et al (80) reported that the lncRNA HERPUD1 intronic transcript of endoplasmic reticulum (ER) stress has a role as an RNA scaffold, facilitating formation of the MRE11-RAD50-NBS1 protein complex. Formation of this complex leads to inhibition of apoptosis of oral squamous cell carcinoma cells induced by ER stress, further promoting tumor growth and invasion. In addition, lncRNAs are able to participate in chromatin modification through scaffolding the modification complex. This mechanism is associated with the function of c-Myc as a transcription factor in BRC. Li et al (81) reported that an oncoprotein, hepatitis B X-interacting protein (HBXIP), directly binds to c-Myc as a co-activator, leading to activation of the transcription of c-Myc target genes. Subsequent experiments that aimed to unravel the mechanism of action reported that HBXIP and lysine-specific demethylase 1 (LSD1) are scaffolded by the lncRNA HOTAIR to form an RNA-protein complex, thereby activating the demethylation of H3K4 through recruiting LSD1 to the promoters of c-Myc target genes. In a separate study (82), a novel lncRNA named as ‘low expressed in bladder cancer stem cells’ (LBCS) was reported to be active in bladder cancer stem cells (BCSCs). LBCS acts as a scaffold to integrate hnRNPK and EZH2, which subsequently form a complex that mediates the induction of H3K27 trimethylation in the SOX2 promoter region, a process that inhibits SOX2 expression and results in suppression of self-renewal and chemotherapeutic resistance of the BCSCs (82).

Taken together, these results suggest that lncRNAs act either as activators or mediators to facilitate interactions between their binding proteins and various biomolecules, thereby expanding the interaction network of cancer-associated RBPs. This feature may explain in part why lncRNAs are implicated in most processes of cancer pathogenesis.

### 3. Regulation of lncRNAs by RBPs in cancer

Regulation of lncRNAs by RBPs has not been widely explored in comparison with the regulation of mRNAs and miRNAs. Advances in techniques for studying protein-RNA interactions, however, have resulted in an increase in the number of studies that explore the direct regulation of lncRNAs through binding of RBPs, a process that is now known to be implicated in the pathogenesis of several diseases, including cancer (15,33,83-85). An in-depth review of this topic has been given elsewhere (86); however, in the current review, the topic is also outlined, as it is an important aspect of lncRNA-RBP interactions, and recent examples are provided.
Regulation of lncRNA expression at the post-transcriptional level. Previous studies on cancer report that changes in expression of RBPs are associated with alterations of lncRNA expression at the post-transcriptional level (86-98), implying that RBPs have a role in regulating the expression of lncRNAs. In addition, direct binding may be the most common mode through which RBPs regulate the stability of lncRNAs in cancer.

RBPs are able to enhance the expression of cancer-associated lncRNA transcripts by maintaining RNA stability through direct binding. For instance, RBP serine/arginine rich splicing factor 1 (SRSF1) is an oncogenic factor of glioma and a key regulator of the cell cycle. SRSF1 directly binds to nuclear-enriched abundant transcript 1 (NEAT1) and maintains RNA stability, whereas NEAT1 is involved in the occurrence and progression of glioma through regulating the cell cycle (87). Furthermore, the classical RBP HuR, which is enriched in several different cancer types, combines with NEAT1_1 and stabilizes it, whereas the abnormal expression of NEAT1_1 is correlated with cell proliferation and invasion in ovarian cancer (88). Although several studies have reported on interactions between RBPs and lncRNA transcripts, the molecular mechanism underlying how RBPs enhance the stability of lncRNAs after their direct combination has yet to be fully elucidated. However, previous studies have suggested the most likely mechanism is that physical binding of RBPs blocks certain specific binding sites associated with the degradation pathway of lncRNA (88-90).

On the other hand, binding of RBPs may lead to an acceleration of the degradation of cancer-linked lncRNAs in cancer, thereby reducing the expression level of lncRNA transcripts and ultimately regulating various cancer phenotypes. Several potential mechanisms of lncRNA degradation induced by binding to RBP have been explored. The first mechanism involves the let-7/Ago2 signaling pathway. Ago2 is the core component of RNA-induced silencing complex (RISC), whereas miRNA let-7 is the key factor that mediates synthesis of RISC induced by Ago2. Therefore, the let-7/Ago2 complex is able to mediate the cleavage of RNA by RISC. For instance, HuR protein has been indicated to be a promoter of mRNA degradation (91) and other studies have reported that it may also induce the degradation of lncRNAs. For instance, previous studies have explored the effect of HuR on lincRNA-p21 (92) and HOTAIR (93). The findings obtained suggested that HuR mediates the interaction between lncRNAs and the let-7/Ago2 complex through direct combination, thereby promoting degradation of the lncRNA. The second mechanism that has been indicated to be involved is the RNA exosome pathway. Exosomes have a central role in RNA metabolism and various types of RNA molecules are degraded through the RNA exosome complex (94,95). Knockdown of poly(A)-binding protein nuclear 1 (PABPN1) in HeLa cells affects the expression level of polyadenylated lncRNAs, including several classic cancer-associated lncRNAs such as NEAT1 and taurine-upregulated gene 1. PABPN1 binds to these lncRNAs and promotes their interaction with RNA-exosome complexes, thereby promoting the degradation of lncRNAs (96). The third mechanism of action that has been implicated involves the carbon catabolite repression 4-negative on TATA-less (CCR4-NOT)-deadenylase complex, which is a highly conserved multifunctional protein complex implicated in RNA decay (97). For example, the RBP IGF2BP1 has been implicated in the degradation of HULC, a lncRNA that is significantly upregulated in human liver cancer. Hammerle et al (98) reported that specific binding occurs between IGF2BP1 and HULC, and verified that elimination of IGF2BP1 may increase the expression level of HULC through prolonging its half-life. IGF2BP1 acts as an adapter protein and recruits the CCR4-NOT complex by binding to CNOT1, the scaffold of the CCR4-NOT deadenylase complex, thereby initiating the degradation of HULC. Therefore, RBPs have been indicated to accelerate the degradation of certain lncRNAs by binding physically with them and either recruiting or mediating specific biomolecules or complexes implicated in RNA degradation.

Regulation of lncRNA localization and transport. The cellular localization of lncRNAs has an important participatory role in their function of gene regulation. Of note, the binding of RBPs to lncRNAs results in changes in their cellular localization. MALAT1 is involved in the maintenance of normal mitochondrial functions (99,100). A study wherein RIP experiments were performed on the RBP HuR and mitochondrial carrier homolog 2 (MTCH2) reported that the two are able to interact with MALAT1, both in isolated mitochondria and in the whole cell, suggesting that MALAT1 is shuttled into mitochondria by physically binding to HuR and MTCH2 complexes (101). Furthermore, the lncRNA RMRP, the RNA component of mitochondrial RNA processing endoribonuclease, is involved in the progression of a variety of human tumors (102-104). A previous study reported on two RBPs, namely HuR and G-rich RNA sequence binding protein (GRSF1), which are implicated in translocation of RNA component of mitochondrial RNA-processing endoribonuclease (RMRP) from the nucleus to mitochondria. HuR binds to RMRP in the nucleus and mediates its nuclear export, whereas GRSF1 binds to RMRP and facilitates its accumulation in the mitochondrial matrix (105). These results suggested that the intracellular distribution of lncRNAs may be mediated via the synergistic action of transport- and localization-associated RBPs.

The structural basis of lncRNA localization has yet to be fully explored; however, the intracellular distribution of lncRNAs may be associated with a specific domain. For instance, U1 small nuclear ribonucleoprotein (U1 snRNPs) interacts extensively with lncRNAs and recruits them to chromatin in a transcription-dependent manner. Yin et al (106) reported that the rapid degradation of SNRNP70, the protein component of U1 snRNPs, reduces the localization of several nascent and polyadenylated lncRNA transcripts in chromatin and significantly disrupts nuclear and genome-wide localization of MALAT1, which has been associated with multiple cancers. Furthermore, this study demonstrated that the U1 recognition motif contained in these lncRNAs may be the factor responsible for their localization. Lubelsky and Ullitsky (107) reported that SINE-derived nuclear localization (SIRLOIN) element with its special sequence has a key role in the nuclear accumulation of lncRNAs. HnRNPK may bind to lncRNAs through SIRLOIN elements and promote their enrichment in, and localization to, the nucleus. In addition, the
RIDL domain is implicated in the subcellular localization of lncRNAs (108). Collectively, these findings indicate that these specific domains frequently mediate interactions between RBPs and lncRNAs, thereby affecting the localization of the lncRNAs.

Furthermore, RBPs are implicated in lncRNA transport through exosomes. Chen et al (109) reported that LNMAT2, an exosomal lncRNA, is able to promote lymphangiogenesis and lymph node metastasis in BLC. Their analysis indicated that LNMAT2 is able to directly bind to the RBP hnRNPA2B1 and was thereby loaded into exosomes secreted by BLC cells. This finding provides a novel research direction for investigating the interactions between RBPs and lncRNAs, and the underlying mechanism(s) merit further attention.

In conclusion, RBPs act as the regulators of the subcellular distribution and transmembrane transport of lncRNAs by binding to specific domains, thereby affecting the regulatory effects of lncRNAs on the progression of cancer.

4. Mediation of lncRNA function

lncRNAs are multi-functional biomolecules that interact with other biomolecules. Binding of RBPs may promote a wider interactome of lncRNAs. Certain RBPs may bind to lncRNAs and mediate the formation of complexes with other proteins. Dangelmaier and Lal (31) named this class of RBPs as ‘adaptor proteins’. Pruszko et al (110) performed RIP experiments using BRC cells and fixed the cells using formaldehyde cross-linking and ultraviolet (UV) approaches. Their results suggested that formaldehyde cross-linked both protein-protein and protein-RNA complexes, whereas UV was only able to cross-link proteins and their directly binding RNA. Of note, antibodies against mutant p53 protein or ID4 protein downregulated lncRNA MALAT1 in the formaldehyde cross-linking group, but not in the UV cross-linking group, indicating an indirect interaction between MALAT1 and mutant p53 or inhibitor of differentiation 4 (ID4) protein. Subsequently, this study revealed that the RBP SRSF1 acts as an adaptor protein that connects MALAT1 and mutant p53 or ID4. Furthermore, lncRNA p53 upregulated regulator of p53 levels (PURPL) suppressed the expression of p53 protein in CRC through blocking the formation of p53-MYB binding protein 1A (MYBBP1A) protein complex, which has been implicated in maintaining p53 stability. RNA pull-down experiments demonstrated an interaction between MYBBP1A and PURPL. However, RIP experiments with UV cross-linking did not detect any direct combination between the two, indicating that the interaction between PURPL and MYBBP1A involved indirect binding. The subsequent steps of this study suggested that HuR mediates the interaction between PURPL and MYBBP1A as an adaptor protein (111). Taken together, these findings indicated that adaptor proteins mediate interactions between lncRNAs and proteins lacking RNA binding ability.

5. Conclusions and future perspectives

lncRNAs and RBPs, in addition to their respective networks, serve an important role in oncogenesis and progression of cancer. Interactions between lncRNAs and RBPs provide the most extensive mode through which they exert their respective biological functions and their interactions affect their respective interaction network with other biomolecules. However, further studies require to be performed to explore the interactions between lncRNAs and RBPs in greater detail. Several studies have reported on the bidirectionality of the regulatory effects between lncRNAs and RBPs, and the polyfunctionality of generalized RBPs, thereby delineating the intricate interactive network that exists among various biomolecules. These studies have also provided a basis for further research. It is anticipated that exploring the common features and key intersections in the interaction network of lncRNAs and RBPs will reveal the underlying mechanisms of oncogenesis and progression of cancer.

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Availability of data and materials

Data sharing is not applicable to this article, as no datasets were generated or analyzed during the current study.

Authors’ contributions

HH and KW conceived the review. HH and LL were involved in the collection of references. HH wrote the manuscript. LL constructed the figure. HH, LL and KW checked and revised the manuscript. HH was responsible for the organization, revision and submission of this manuscript. All authors read and approved the final manuscript. Data authentication is not applicable.

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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