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Long non-coding RNAs in cancer

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Long non-coding RNAs (lncRNAs) are a group of RNA transcripts that exceed 200 nt in length, yet lack significant open reading frames (ORFs) [1–4]. In contrast to small non-coding RNAs (ncRNAs), such as microRNAs (miRNAs) [4–23], small interfering RNAs (siRNAs) [24–31] and transfer RNAs (tRNAs) [32–34], there are thousands of lncRNA genes discovered during the past three years in the human genome and most of their functions remain elusive. The long nucleotide chain of lncRNAs can either form a complex spatial structure and interact with protein factors, or provide a large segment for the concurrent binding of many molecules that collectively participate in genomic imprinting, X-chromosome silencing, chromosome modification, intranuclear transport, transcriptional activation and interference, thereby regulating cell growth, differentiation, development, senescence and death [35].

Accumulating evidence supports that lncRNAs participate in many physiological processes by modulating gene expression at the epigenetic, transcriptional and post-transcriptional levels. LncRNAs regulate gene expression at the epigenetic level through DNA methylation or demethylation, RNA interference, histone modifications, chromatin remodeling, etc. [36–42]. At the transcriptional level, lncRNAs depends on the relative position and sequence features of the lncRNA and the target gene to regulate gene expression. Khps1a is an lncRNA that is transcribed near the CpG island of the oncogene *sphingosine kinase 1* (*SphK1*). Through binding to 3 CC(A/T)GG sites in the tissue-dependent differentially methylated region (T-DMR) of *SphK1*, Khps1a induces the demethylation of the CpG island, resulting in increased expression of *SphK1* [43]. Another example is the 3′ end of yeast lncRNA Srg1, which overlaps the promoter of the target gene *Ser3* and inhibits *Ser3* expression by occupying the binding site for transcription initiation factors in the *Ser3* promoter [44]. At the transcriptional level, some lncRNAs inhibit the transcription of target genes by binding to the promoters of target genes and forming stable DNA-RNA triplex complexes [45], while others cooperate with transcription modulators in transcriptional regulation and interfere with the formation of the transcription initiation complex to repress transcription initiation and to rapidly alter gene expression patterns [46]. Post-transcriptionally, the formation of a RNA dimer via complementary base pairing between the lncRNA and the

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target mRNA can block the binding sites of transcription factors and processing-related factors, which regulate mRNA splicing, translation and degradation [47]. Some lncRNAs bind miRNAs and competitively inhibit the interaction between miRNAs and target mRNAs to modulate gene expression. Furthermore, lncRNAs can function as structural components of larger RNA-protein complexes, modulate the activity and subcellular localization of proteins, and thus play additional specific roles [36].

Deregulated expression of lncRNAs has been found in a variety of cancers [48]. Profiling lncRNA expression in five cases of HBV-associated hepatocellular carcinoma tissue and non-cancerous tissue, Yang *et al*. [49] found that 174 lncRNAs were deregulated in hepatocellular carcinoma. Khaitan *et al*. [50] discovered that 77 lncRNAs were deregulated in the melanoma cell line WM1552C; the authors further analyzed lncRNA expression in 29 melanoma patient samples and 6 normal skin samples and identified 4 lncRNAs that were deregulated in both the WM1552C cells and the melanoma patient specimens. These data implicate lncRNAs in carcinogenesis and tumor progression. However, the molecular mechanisms by which most lncRNAs influence oncogenesis are unknown and require further investigation. We discuss several tumor-associated lncRNAs: H19, ANRIL, MALAT1, HOTAIR and MEG3.

The lncRNA H19, which is 2.3 kb in length and encoded by the maternally imprinted gene *H19* on chromosome 11p15.5, was the first lncRNA determined to be associated with cancer. H19 rapidly decreases in most tissues after birth, but is reactivated during carcinogenesis. H19 expression is elevated in several types of cancer, including hepatocellular, bladder and breast carcinomas, which suggests an oncogenic function [51]. The oncogene *c-Myc* directly activates H19 by binding to the *H19* promoter [52], while the tumor suppressor p53 decreases H19 expression [48]. Either direct or indirect binding of the transcription factor E2F1 to the *H19* gene promoter stimulates cells to enter S phase and accelerates cell cycle progression, resulting in the proliferation of breast cancer cells [53]. In human colorectal cancer, miR-675 is processed from the first exon of *H19* and this miRNA inhibits the expression of the tumor suppressor gene *retinoblastoma (RB)* to play an oncogenic role [54]. In contrast to its oncogenic effect, H19 appears to participate in tumor suppression in other contexts. Over-expression of H19 in two embryonic tumor cell lines, RD and G401, inhibits cell proliferation and tumorigenesis. In a mouse model of teratocarcinoma, embryos lacking H19 grew larger tumors than those expressing H19. In a similar model with hepatocarcinoma, mice developed tumor much earlier when H19 was absent [51].

ANRIL (antisense non-coding RNA in the INK4 locus) is an antisense lncRNA encoded by the INK4 locus of the *INK4B/ARF/INK4A* gene cluster on chromosome 9p21.3 and processed into multiple transcripts, including an unspliced transcript of 34.8 kb termed p15AS [55]. ANRIL is considered an oncogenic lncRNA due to its increased expression in leukemia and prostate cancer [36]. By regulating the expression of the tumor suppressor genes *p15/CDKN2B*, *p16/CDKN2A* and *p14/ARF* in the *INK4B/ARF/INK4A* gene cluster, ANRIL modulates cell cycle progression and cellular senescence and subsequently promotes tumorigenesis [56]. ANRIL interacts with the CBX7 component of polycomb repressive complex 1 (PRC1) and recruits PRC1 to the *INK4B/ARF/INK4A* gene cluster, where PRC1 induces changes in the chromatin structure that silence the *INK4B/ARF/INK4A* gene cluster [36].

The lncRNA MALAT1 (metastasis-associated lung adenocarcinoma transcript 1), also known as NEAT2, is 7.5 kb in length and encoded by the *MALAT1* gene located on chromosome 11q13.1. Cellular MALAT1 can be post-transcriptionally processed to yield the short, highly conserved, tRNA-like molecule mascRNA and the long MALAT1 transcript, which contains a poly(A) tail-like moiety [57]. MALAT1 is expressed in normal human tissues and exhibits increased expression in cancers of the breast, prostate, colon, liver, lung and others [58]. The expression level of MALAT1 in the metastatic tumors of non-small cell lung cancer (NSCLC) patients is three times higher than that of patients lacking metastatic tumors, and patients harboring tumors with elevated MALAT1 expression have a poor prognosis [59]. MALAT1 promotes lung adenocarcinoma cell migration *in vitro* by regulating cell motility-related genes at the transcriptional and/or post-transcriptional level [60]. The inhibition of MALAT1 reduces the proliferative and invasive potential of cervical cancer cells *in vitro* [61]. MALAT1 remains in the nucleus and localizes to nuclear speckles, where pre-mRNA processing occurs. A recent study revealed that MALAT1 regulates the alternative splicing of pre-mRNAs by modulating the activation of serine/arginine splicing factors [62]. This result implies that MALAT1 regulates the post-transcriptional processing or modification of RNA. MALAT1 binds to PSF (polypyrimidine tract binding protein-associated splicing factor) and prevents PSF from binding to the transcriptional regulatory region of the oncogene *CAGE6*, which stimulates the abundant transcription of *GAGE6* and thus promotes tumorigenesis [63].

HOTAIR (HOX antisense intergenic RNA), which is 2158 nt in length, is an antisense lncRNA transcribed near the HOXC loci on chromosome 12q13.13 [37]. HOTAIR was discovered to be highly over-expressed in primary breast epithelial tumors and induced the invasion and metastasis of breast cancer [64]. The expression level of HOTAIR in hepatocellular carcinoma tissues was also higher than that of adjacent non-cancerous tissues, and the high levels of HOTAIR expression correlated with recurrence and a poor survival rate in liver cancer patients that received liver transplants [65]. In addition, decreasing the expression of HOTAIR in breast cancer and hepatocellular carcinoma cell lines inhibited tumor invasion [64,65]. Fur-

thermore, inhibition of HOTAIR sensitized tumor cells to tumor necrosis factor α (TNFα)-induced apoptosis, as well as apoptosis induced by treatment with chemotherapeutic agents cisplatin and doxorubicin [65]. HOTAIR functions as a molecular scaffold, binding at least two distinct histone modification complexes. The 5′ region of HOTAIR binds the PRC2 complex responsible for H3K27 methylation, and the 3′ region of HOTAIR binds the LSD1/CoREST/REST complex that mediates the demethylation of H3K4 [1]. HOTAIR recruits the PRC2 complex to specific target genes on a genome-wide scale, thereby facilitating abnormal H3K27 methylation and the epigenetic silencing of tumor metastasis suppressor genes, including *JAM2*, *PCDH10*, and *PCDHB5*. Furthermore, the HOTAIR-mediated recruitment of PRC2 induces the expression of pro-metastasis genes, such as *ABL2*, *SNAIL*, and *Laminin*, thereby promoting breast cancer metastasis [64].

MEG3 (maternally expressed gene 3), 1.6 kb in length, is encoded by the *MEG3* gene of the DLK1/MEG3 locus on human chromosome 14q32.3. The *MEG3* gene is a maternally imprinted gene composed of 10 exons, and 12 MEG3 isoforms have been detected to date [66]. MEG3 is expressed in multi-organs and exhibits particularly high expression levels in the brain and the pituitary gland; however, MEG3 expression is reduced or absent in some tumors and tumor cell lines. Multiple mechanisms, including gene deletion, hypermethylation of the promoter and the intergenic region, contribute to the loss of MEG3 expression in tumors [67]. MEG3 inhibits the proliferation of tumor cells and modulates tumor angiogenesis by regulating p53, MDM2, Rb, $p16^{INK4A}$, Notch, VEGF and their signaling pathways, thereby suppressing tumorigenesis [68]. MDM2 is an important negative regulator of the p53 protein, and both p53 and MDM2 are target genes of MEG3 [69]. In tumor cells, MEG3 can either directly increase p53 expression or indirectly enhance p53 expression through targeted inhibition of MDM2 [69]. The activity of p53 requires the transcription of the full length MEG3 transcript, but not the translation of the MEG3 protein. Intriguingly, MEG3 fails to stimulate expression of the p53 target gene $p21^{Cip1}$, but can increase the expression of the cell proliferation inhibitory gene *GDF15* through p53 [69]. Further studies revealed that MEG3 enhances p53 binding to the *GDF15* promoter but not to the $p21^{Cip1}$ promoter [69]. Therefore, MEG3 activates p53 and selectively induces the expression of p53 target genes to inhibit the proliferation of tumor cells. Furthermore, MEG3-mediated functional activation of p53 depends on MEG3 secondary structure rather than the primary sequence of MEG3 [66]. MEG3 also suppresses tumor cell proliferation directly by regulating Rb phosphorylation and indirectly by activating the tumor suppressor gene $p16^{INK4A}$, which positively regulates *Rb* [68,70]. In a *Meg3* knock-out mouse model, Meg3 was discovered to suppress angiogenesis by regulating VEGF signaling pathways [71]. Additionally, Meg3 regulates cell proliferation, differentiation and other important processes by modulating Notch signaling pathways to suppress tumorigenesis [71].

There are other lncRNAs that participate in carcinogenesis and cancer progression, including Zeb2 NAT (natural antisense transcripts, also known as antisense RNA), p21 NAT, CCND1 ncRNA, etc. The *Zeb2* gene is a transcriptional repressor of *E-cadherin*. A recent study demonstrated that the NAT of *Zeb2* (Zeb2 NAT, also known as Sip1 NAT) increases Zeb2 protein expression by regulating splicing and inhibiting *E-cadherin* expression in mesenchymal cells, which subsequently induces epithelial-to-mesenchymal transition (EMT) and promotes tumor metastasis [47]. The lncRNA p21 NAT, which is the NAT of the tumor suppressor *p21/CDKN1A*, cooperates with Ago-1 to induce histone H3K27 methylation of the *p21/CDKN1A* promoter region, thereby inhibiting p21 expression and promoting tumorigenesis [72]. *CCND1*, encoding cyclin D1 protein, is an important cell cycle regulatory gene that, when over-expressed, induces malignant hyperplasia and promotes tumorigenesis. When cells are subjected to DNA damage, the lncRNA CCND1 ncRNA is transcribed from the regulatory sequence of the *CCND1* gene promoter region [73]. The CCND1 ncRNA recruits the RNA-binding protein TLS (translocated in liposarcoma) to the *CCND1* promoter region and converts the TLS protein from the inactive conformation into the active form. The modified TLS then binds to and inhibits CREB-binding protein (CBP) and p300 histone acetyltransferase activities, thereby reducing the expression of *CCND1* [73] and suppressing tumorigenesis.

Many important biological functions of lncRNAs have been discovered recently as lncRNAs have become another hotspot in the field of molecular oncology. Substantial evidence indicates that lncRNAs participate in all steps of tumor initiation and development; therefore, thorough elucidation of their functions and molecular mechanisms are of great importance in the diagnosis and treatment of cancer. For example, the lncRNA DD3 demonstrated greater specificity than serum prostate-specific antigen (PSA) in predicting prostate tumors and is being developed into a new diagnostic marker for prostate cancer [74]. HOTAIR may serve as a potential biomarker for the lymph node metastasis of hepatocellular carcinoma [65]. Additionally, preventing the interaction between HOTAIR and the PRC2 or LSD1 complex may limit the metastatic potential of breast cancer cells [48]. Although our current knowledge on lncRNAs is only the tip of the iceberg, novel methods and technology will eventually lift the mysterious veil covering lncRNAs, thereby enabling the development of new cancer therapeutic strategies.

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