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HOTAIR: a cancer-related long non-coding RNA

Minireview

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Long non-coding RNA was dismissed as merely transcriptional "noise" in the past decades. Numerous researches have shown that lncRNAs regulated gene expression at the epigenetic level. Moreover, lncRNAs played important roles in proliferation, apoptosis and invasiveness of tumor cells, and participated in metastatic capacity of cancers. Recent studies revealed HOX transcript antisense RNA, a lncRNA with regulatory functions of transcription, could bind PRC2 and LSD1/CoREST/REST complexes and direct to the specific gene sites, resulted in H3K27 methylation and H3K4 demethylation and ultimately gene silencing. Aberrant HOTAIR expression was associated with various sites of cancers such as breast, hepatocellular, gastric, colorectal, pancreatic et al; and affected survival and prognosis of cancer patients. In this review, we introduce an overall view of HOTAIR by describing the known molecular mechanisms and potential functions of HOTAIR and summarizing the latest progresses on the research of HOTAIR in various human cancers.

Key words: HOTAIR, LncRNA, HOX genes, cancer

Long non-coding RNAs (LncRNAs) are commonly defined as RNA moleculars larger than 200 nucleotides. LncRNA was first found among transcribed DNA product of the mouse by Okazaki [1]. Many identified lncRNAs were transcribed by RNA polymerase II (RNA pol II) and spliced [2, 3]. One view existed in the past few decades that lncRNAs were as diverse as their better known counterpart messenger RNAs (mRNAs), having no protein-coding capacity, were described as transcriptional "noise" [4, 5, 6]. However, a number of studies have shown that some lncRNAs were involved in embryogenesis and differentiation [7, 8]. These lncRNAs are expressed in specific cell types [9, 10, 11] and located in specific subcellular compartments [12, 13, 14]. Moreover, recent studies have indicated that lncRNAs participated in a wide range of biological pathways and cellular processes. They could regulate gene expression and function, including dosage compensation [15, 16], genome rearrangement [17], chromatin modifications [7, 18, 19], gene imprinting [20, 21, 22], alternative splicing [23], nuclear-cytoplasmic trafficking [24, 25, 26], cell cycle control [27, 28, 29] and inactivation of major tumor suppressor genes [30, 31]. Wang et al [32] summarized the functions of lncRNAs as signals [33], decoys [34, 35], guides [15] and scaffolds [18, 36].

HOX transcript antisense RNA (HOTAIR) is a lncRNA which has regulatory functions of transcription and are transcribed from the antisense strand of homeobox C gene locus in chromosome 12. HOTAIR recruits Polycomb Repressive Complex 2 (PRC2) and histone demethylase complex [LSD1 (lysine specific demethylase 1)/CoREST (Co-repressor of RE1-silencing transcription factor)/REST]; then leads to histone H3 tri-methylated at lysine 27 (H3K27me3) and histone H3 dimethyl Lys4 (H3K4me2); consequently results in gene silencing. In addition to its scaffold function to assemble transcription regulators, and a latest study reported that HOTAIR could also serve as a platform to control protein levels via the ubiquitin–proteasome pathway. HOTAIR facilitated the ubiquitination of Ataxin-1 by Dzip3 and Snurportin-1 by Mex3b, and then accelerated their degradation. Moreover, HOTAIR levels were highly upregulated in senescent cells. It

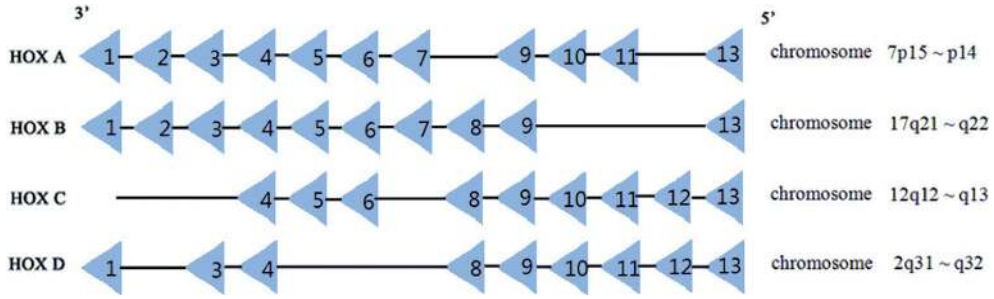

Figure 1. Structures of HOX genes.

could cause rapid decay of targets Ataxin-1 and Snurportin-1, and prevented premature senescence [37].

As more and more attention has been focused on HOTAIR, it has been revealed that HOTAIR had significant relationships with a variety of cancers such as breast [38], hepatocellular [39], colorectal [40], pancreatic [41], etc. The expression level of HOTAIR was associated with the viability, proliferation and invasion of tumor cells, and effected the survival and prognosis of cancer patients. Although the precise mechanisms of HOTAIR in cancer progression are not entirely clear, it has become increasingly obvious that HOTAIR potentially associated with cancer development and metastasis. With HOTAIR becomes a hot research topic recently, our review introduces previous studies on HOTAIR and HOTAIR-related cancers, describes the known functions and possible underlying molecular mechanisms of HOTAIR and points out the current questions and prospects.

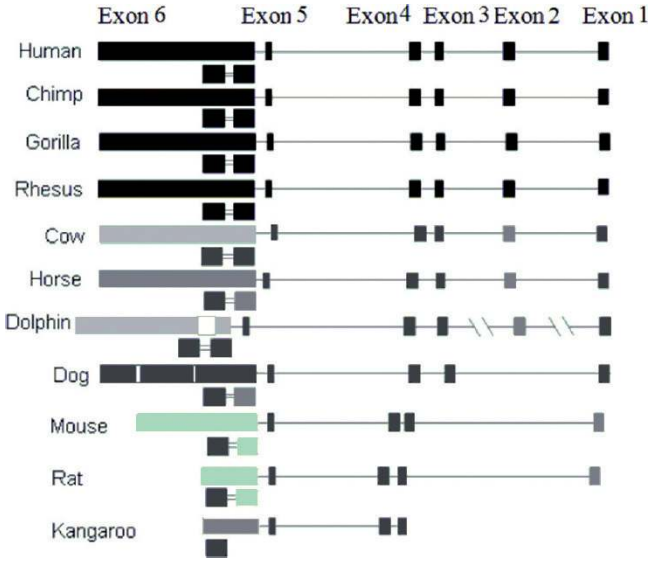

Figure 2. Structures of HOTAIR exons.
Exon1, exon3, exon4, exon5 and domain B of exon6 are better conserved than exon2, exon6 and domain A of exon6 (indicated by the darkness of the boxes). The two boxes under each exon6 are domain A (right side) and domain B (left side), linked by a double line indicating a gap of 130bp (Figure modified from Ref 54).

Homeobox genes

Homeobox genes (HOX genes) were discovered in Drosophila by Lewis in 1978 [42]. HOX gene encodes for a 60 amino acid DNA-binding domain called the homeodomain, which is a 180-bp DNA sequence and highly conserved in evolution. There are 39 HOX genes in mammals, which are divided into A, B, C, D four clusters. Each cluster contains 9 to 11 genes Figure 1. HOX genes are demarcated by broad chromosomal domains of transcriptional accessibility, marked by extensive occupancy of RNA polymerase II and H3K4me2; in a mutually exclusive way, by occupancy of PRC2 and H3K27me37. By the way of above, HOX genes can affect genes transcription by specifying the positional identities of chromosomes [43]. Aberrant expressions of HOX genes may affect cells differentiation and ontogeny, causing abnormal tissues and organs, and even contribute to a variety of tumors, such as ovarian cancer [44], gastric cancer [45], colorectal cancer [46, 47], neuroblastoma [48], kidney cancer [49], prostate cancers [50] and hematological malignancies [51, 52, 53].

HOX transcript antisense RNA

HOTAIR is a long noncoding RNA 2158-nucleotides long, located on chromosome 12q13.13, and transcribed in an antisense manner with respect to the canonical HOXC genes. HOTAIR is highly conserved in primates and evolves faster than its neighbouring HoxC genes. Strand-specific RT-PCR analysis confirmed that only one strand of HOTAIR, antisense to HOXC genes, was transcribed. HOTAIR was preferentially expressed in posterior and distal sites. Computational analysis of HOTAIR secondary structure did not reveal obvious stem loops suggestive of pre-miRNAs. Northern blot analysis of size-fractionated RNA showed no evidence of small RNA products, which were suggestive of micro RNA or small interfering RNA (siRNA) production [7].

Figure 2 showes HOTAIR includes five short exons and a long exon. Different exons have different transition/

transversion rate ratio, different shape parameter of the gamma distribution and different nucleotide substitution rates between clades. All above indicate that different exons of HOTAIR have asynchronous evolution in mammals. Structure prediction vertified that the sequences and structures of the 5' end exon 1 and the 3' end domain B of exon 6 were highly conserved in mammals. It is considered that the two domains are the functional domains of HOTAIR, which can interact with polycomb protein and play a wide range of biological functions [54].

Molecular mechanisms of HOTAIR

Rinn et al [7] investigated the function of HOTAIR and found that siRNA-mediated depletion of HOTAIR had little effect on the transcription of HOXC locus on chromosome 12, while led to dramatic transcriptional activation of the HOXD locus on chromosome 2. Further study revealed depletion of HOTAIR resulted in loss of H3K27Me3 and Suz12 occupancy over the HOXD locus. Therefore, it was speculated that HOTAIR was selectively required to target PRC2 occupancy; thus, induced H3K27 trimethyation and silenced transcription of the HOXD locus. PRC2 first recruited to specific genomic locations to catalyze H3K27me3; methylated-H3K27 then served as a recognition site to further recruit PRC1; which in turn introduced H2AK119ub1 marks and impeded RNA polymerase II elongation [55, 56]. EZH2 (enhancer of zeste homolog 2) was the catalytic subunit of PRC2, which directly attached on HOTAIR [57]. Its activity required binding to SUZ12 (suppressor of zeste 12) and EED (embryonic ectoderm development). In addition to PRC2, Tsai et al [58] found that HOTAIR could also bind to LSD1. LSD1 was a demethylase which could form a complex with CoREST and REST, and mediated enzymatic demethylation of H3K4me2. H3K4 demethylation was widely associated with transcriptional inactivation.

Chromatin Immunoprecipitation–chip (ChIP-chip) showed HOTAIR knockdown caused loss of SUZ12 and LSD1 occupancy in proximal promoters of HOXD genes; these regions correspondingly lost H3K27me3 and gained H3K4me2, the respective histone methylation products of PRC2 and LSD1 complexes. The loss of H3K27me3 occurred across broad domains encompassing multiple HOXD genes and intergenic regions, while the gain of H3K4me2 was concentrated near the transcriptional start sites of HOXD genes. Utilizing a series of HOTAIR deletion mutants, the PRC2 binding activity mapped to the first 300 bp of HOTAIR, while the LSD1 complex binding activity mapped to the last 646 bp. Therefore, a commonly recognized molecular mechanisms of HOTAIR is that the 5' domain of HOTAIR can bind to PRC2, while the 3' domain of HOTAIR can bind to the LSD1/CoREST/REST complex; after that, the complexes are targeted and assembled to the HOXD locus; and coordinately regulate histone H3K27 methylation and histone H3K4 demethylation; consequently, the transcription across 40 kb of the HOXD locus is silenced in trans by DNA methylation Figure 3. In addition to HOXD locus, Tsai et al also analyzed the genome-wide promoter occupancy of PRC2 and LSD1complexes, and uncovered that 721 promoters were targeted by both complexes. 40% of these promoters (289) displayed a corresponding loss of PRC2 and LSD1 occupancy in response to HORAIR knockdown. These results indicated

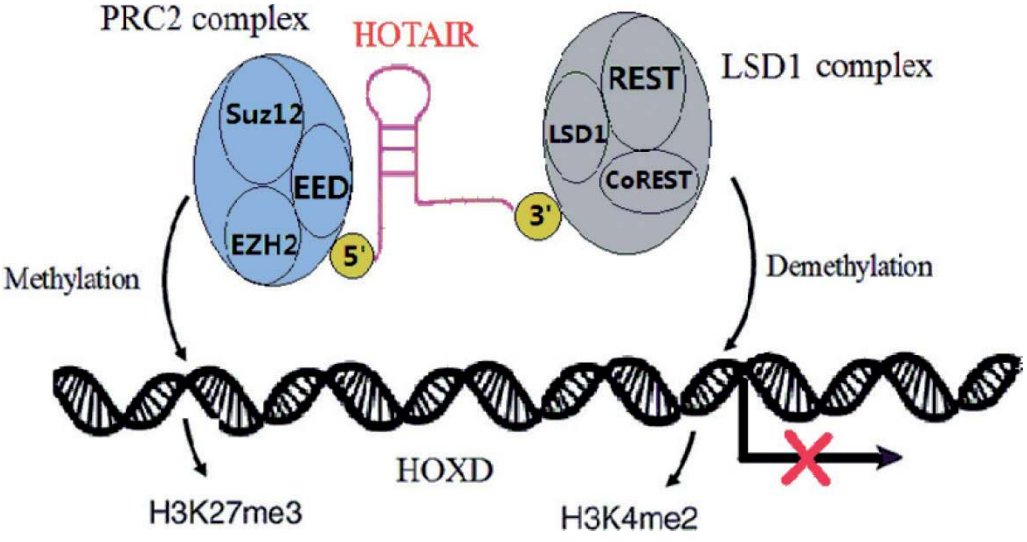

Figure 3. The mechanism of HOTAIR-mediated gene silencing.
PRC2 and LSD1-CoREST complexes bind to the 5' and 3' portions of HOTAIR respectively. The resulting molecular complex is bound to the HOXD locus; coordinately regulate the histone modifications H3K27me3 trimethylation and H3K4me2 demethylation; which in turn, silence expression of the target genes.

Table 1. Related cancers and potential functions of HOTAIR.

Cancer	Potential functions of HOTAIR	References
Breast Cancer	In MCF7 cells, HOTAIR expression was associated with Bcl2 and BID expression, which contribute to cytochrome c release and apoptotic cell death. Over expression of HOTAIR induced localization of PRC2 on 854 new genes, subsequently changed these gene expressions. Part of these genes are associated with inhibiting breast cancer progression, including HOXD10, PRG1, PCDH, JAM2 and EPHA1.	38, 59, 67, 68
Colorectal Cancer	Upregulated expression of HOTAIR induced SUZ12, H3K27me3, EZH2 and PRC2 occupancy in CRCs.	40
Hepatocellular Cancer	Knockdown of HOTAIR reduced the levels of MMP-9 and VEGF, which play important roles in cell motility and metastasis.	39, 69, 70
Gastric Cancer	Expression of HOTAIR in gastric cancer was associated with dysregulation of some EMT (epithelial- mesenchymal transition) related genes and metastasis related genes (ICAM-1, MMP1, MMP3, MMP9), as well as expression of snail, a transcription factor (TF) involved in various EMT processes.	71, 72, 73
Gastrointestinal Stromal Tumor	Gene expression microarray analysis revealed that a total of 1,424 genes were upregulated by HOTAIR siRNA, including PCHD10, SEMA6A, STK17B.	74
Pancreatic Cancer	HOTAIR expression regulated some significant gene sets in Panc1 cells, which were related to the cell cycle progression and viability. Knockdown of PRC2 components (EZH2 and Suz12) as well as HOTAIR in Panc1 and L3.6pL cells similarly induced expression of GDF15, which is a growth inhibitory gene.	41, 75
Lung Cancer	HOTAIR expression was associated with the levels of matrix metalloproteinases (MMP2, MMP9) and HOXA5. MMPs are involved in degrading the extracellular matrix (ECM) and HOXA5 is involved in NSCLC cell migration and invasion.	78, 79, 81
Laryngeal Squamous Cell Carcinoma	Promoter methylation analysis suggested that HOTAIR was involved in regulating PTEN methylation in Hep-2 cells, which may be a potential oncogenic mechanism of HOTAIR in LSCC.	82
Nasopharyngeal Carcinoma	HOTAIR expression was associated with the invasive potential of cells, and cells with high invasive potential (5–8F, S18, CEN2) appeared higher expression levels of HOTAIR than cells with low invasive potential (6–10B, S26, CNE1).	83
Esophageal Squamous Cell Carcinoma	HOTAIR reprogrammed the gene expression profile of ESCC cells, including genes involved in cell migration and cell cycle.	84, 86
Endometrial Carcinoma	A higher HOTAIR expression appeared correlated with the depth of myometrial invasion and lymphovascular space invasion.	85
Mesenchymal Glioma	HOTAIR expression was associated with gene sets involved in cell cycle progression. HOTAIR reduction induced colony formation suppression, cell cycle G0/G1 arrest, and orthotopic tumor growth inhibition.	88
Melanoma	Knockdown of HOTAIR suppressed the degradation of gelatin matrix, which is associated with tumor cell invasion.	89

that HOTAIR-mediated assembly and targeting of PRC2 and LSD1 complexes could be a general mechanism for gene silencing across the genome.

Breast cancer

It was detected by qRT-PCR (quantitative real-time PCR) that in primary breast tumors and metastases, HOTAIR was over expressed from hundreds to nearly two thousand- fold than normal breast epithelia Figure 4. Multivariate analysis showed that HOTAIR was an independent mark for prognostic stratification of metastasis and death, besides known clinical risk factors such as tumor size, stage and hormone receptor status. Enforced expression of HOTAIR in four different breast cancer cells (MCF-10, MCF-7, SK-BR3, MDA-MB-231) could increase cell invasion through matrigel. HOTAIR-expressing in MDA-MB-231 cells increased the rate of primary tumor growth in vivo; moreover, it enhanced metastasis to lung. Conversely, HOTAIR siRNAs in MCF7 decreased its invasiveness [38]. Bhan [59] and colleagues found that HOTAIR knockdown in MCF7 cells resulted in upregulation of Bcl2 and BID expression, which contributed to cytochrome c release [60] and apoptotic cell death [61]. Further study demonstrated that HOTAIR expression was an estrogen-responsive gene expression and could be induced by E2 via estrogen receptors (ERs) and ER coactivators. ChIP-chip observed that overexpression of HOTAIR induced localization of PRC2 on 854 new genes, subsequently changed these gene expressions. Part of these genes were verified associated with inhibiting breast cancer progression, including HOXD10 [62], PRG1, PCDH [63], JAM2 [64] and EPHA1 [65, 66]. Another study found that both HOTAIR and EZH2 appeared highly expressed in the breast cancer metastasis; and co-expression of HOTAIR and EZH2 was prone to a worse outcome [67]. In addition, Lu et al [68] analyzed HOTAIR expression and DNA methylation in tissues from 348 primary breast cancers, and found heterogeneous expression of HOTAIR in primary breast cancer, which was consistent with previous reports. However, they did not find

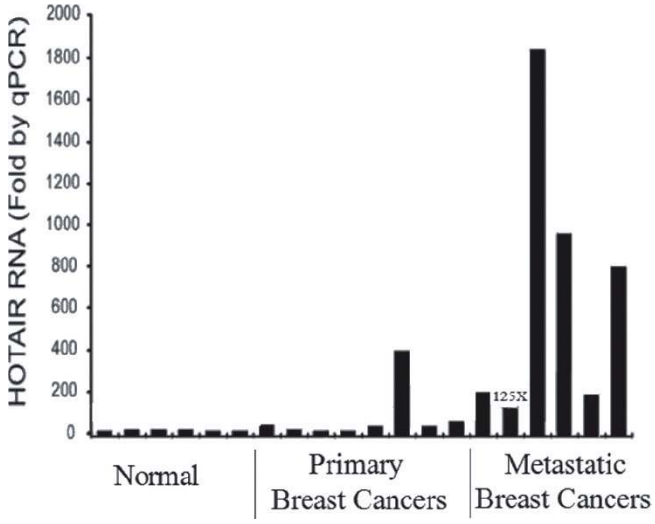

Figure 4. qRT-PCR of HOTAIR abundance in normal breast epithelia and breast cancers.
Metastatic cancers had a minimum 125-fold higher level of HOTAIR than normal breast
Epithelia (Figure modified from Ref 38).

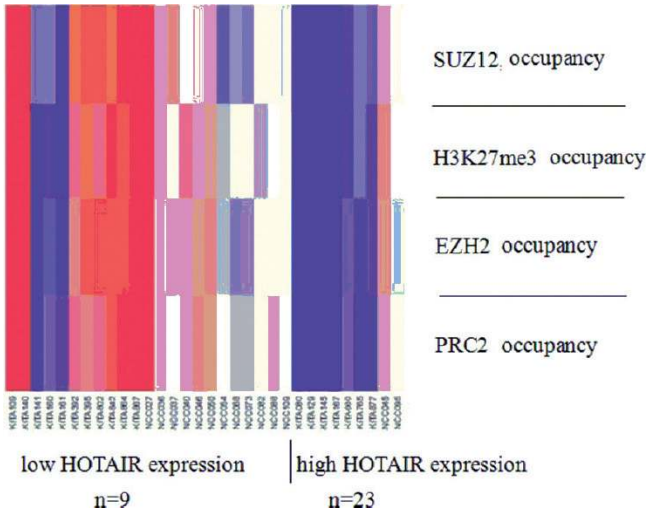

Figure 5. Heat map of the gene expression averages for 32 CRC samples. The enriched gene expression averages were classified by high and low HOTAIR expression levels. Enriched gene expression signatures of HOTAIR-induced SUZ12, H3K27me3, EZH2, and PRC2 occupancy were described by red and blue colors. The red and blue colors indicate high and low expression, respectively (Figure modified from Ref 40).

significant associations of HOTAIR expression with clinical or pathologic characteristics. Interestingly, in multivariate analyses with the control of other clinical characteristics and therapy status, patients with high levels of HOTAIR expression had lower risks of relapse and death than those with low expression. This result indicated that clinicopathological features and therapy treatments could modify the effect of HOTAIR. Based on the above findings, it is considered that HOTAIR can be used as an independent predictor of breast cancer metastasis and prognosis, but it still needs further verification, and the interdependence between HOTAIR and PRC2 may be able to serve as a potential target for the treatment of breast cancer.

Colorectal cancer

In colorectal cancers (CRCs), HOTAIR expression was also higher in cancerous tissues than corresponding noncancerous ones, and HOTAIR expression was associated with the clinical and pathological manifestations. Moreover, high HOTAIR expression showed significantly more inclined to liver metastasis and poorer prognosis [40]. GSEA based on cDNA microarray showed upregulated expression of HOTAIR similarly induced SUZ12, H3K27me3, EZH2, and PRC2 occupancy as in breast cancers Figure 5.

Hepatocellular cancer

The expression levels of HOTAIR in 4 kinds of liver cancer cell lines (SMMC-7721, HepG2, Bel-7402, HCCLM3) were detected higher than normal liver cell lines; and paired primary tumor tissues exhibited higher HOTAIR expression than adjacent nontumorous ones [39]. Moreover, overexpression of HOTAIR in HCC patients was associated with lower 3-year cumulative recurrence-free survival and shorter recurrence-free survival after LT in HCCs. Knockdown of HOTAIR significantly decreased HepG2 cells viability and invasiveness, and increased susceptibility to apoptotic stimuli TNF-a as well as chemotherapeutic drug cisplatin and doxorubicin. It indicated that HOTAIR could be a therapeutical target to improve clinical therapies. HOTAIR expression was also associated with lymph node metastasis and tumor size in HCC patients [69]. Knockdown of HOTAIR reduced the levels of MMP-9 and VEGF [70], which play important roles in cell motility and metastasis. Gene set enrichment analysis (GSEA) showed the expression profiles of localization of H3K27me3 and EZH2 were not significantly associated with HOTAIR expression in HCCs, unlike that noted in breast and colorectal cancers; however, this outcome needed to be further confirmed.

Gastric cancer

Endo [71] and colleagues, using qRT-PCR, discovered that HOTAIR expression were significantly higher in carcinoma lesions compared to non-cancerous lesions in gastric cancer patients Figure 6. High HOTAIR expression was associated with tumor stage, lymph node metastasis, venous invasion and poor survival [72]. Moreover, the anchorage-independent growth and peritoneal dissemi-

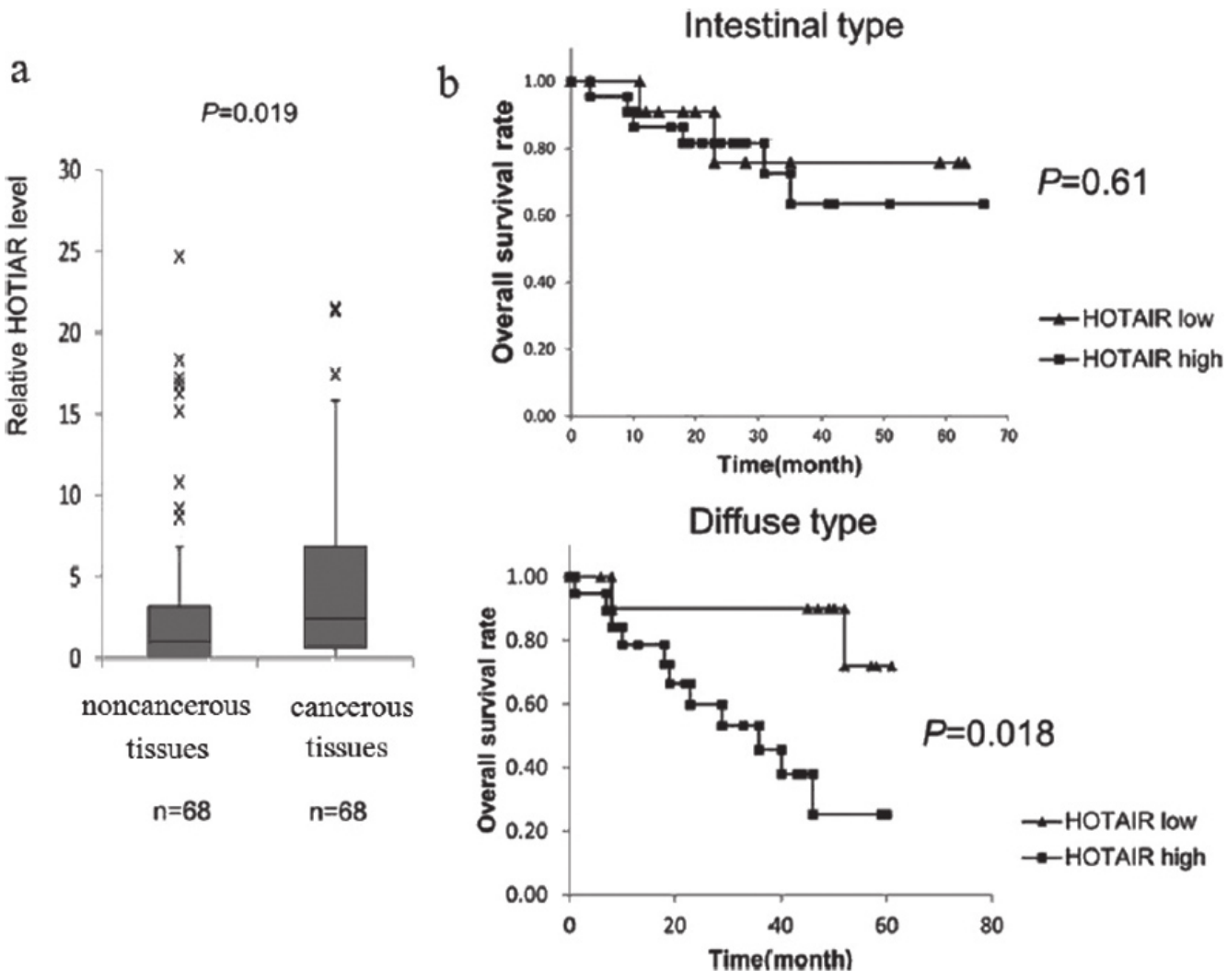

Figure 6. Relative HOTAIR level in cancerous and adjacent noncancerous tissues.
(a) The HOTAIR expression levels of cancerous and adjacent noncancerous tissues from the gastric cancer patients were examined by qRT-PCR and normalized by the GAPDH expression level. The expression levels of HOTAIR were significantly higher in carcinoma tissues compared to those of non-cancerous tissues. (b) The overall survival between high and low HOTAIR expression groups in intestinal and diffuse types of gastric cancer. A significantly short overall survival was found in the diffuse type gastric cancer (Figure modified from Ref 71).

nation of gastric cancer were promoted by overexpression of HOTAIR but inihibited when HOTAIR expression was knockdown by its targeted shRNA (shHOTAIR). Similar conclusions were reported by Xu [73] and co-workers, they found that some EMT (epithelial- mesenchymal transition) related genes as well as some metastasis related genes (ICAM-1, MMP1, MMP3, MMP9) were misregulated in gastric cancer with high expression of HOTAIR. Further study discovered that deletion of HOTAIR could reverse EMT and the expression of snail, which decreased markedly when HOTAIR knockdown. Snail is a transcription factor (TF) involved in various EMT processes. The invasiveness of gastric cancer cell suppressed by HOTAIR siRNA could be restored by exogenous snail, and the EMT reversed by HOTAIR knockdown could also be restored by exogenous snail expression.

Gastrointestinal stromal tumor and pancreatic cancer

It was reported that over expression of HOTAIR was associated with high-risk grade, metastasis and poor overall survival in gastrointestinal stromal tumor (GIST) and pancreatic cancer patients [74, 75]. Kim [41] and colleagues found knocking down HOTAIR expression increased expression of 454 genes and decreased expression of 552 genes in pancreatic cancer cell line, including

20 significant gene sets in Panc1 cells, 10 of which were related to the cell cycle progression and viability. In GIST cells, a total of 1,424 genes were upregulated by HOTAIR siRNA (>2-fold), including a number of reported HOTAIR target genes (PCHD10, SEMA6A, STK17B) [75]. In additiona, comparison of the genes induced or repressed by HOTAIR knockdown or overexpression in Panc1 cells and MDA-MB-231 cells showed that HOTAIR regulated significantly different sets of genes in these two cells. Moreover, study found that knockdown of PRC2 components (EZH2 and Suz12), as well as knockdown of HOTAIR in Panc1 and L3.6pL cells similarly induced expression of GDF15, which is a growth inhibitory gene [76, 77]. ChIP analysis showed that primers directed at the proximal region of the GDF15 promoter detected H3K27 trimethylation and EZH2 binding but not RNA pol II interactions in Panc1 cells transfected with control siRNA; In contrast, knockdown of HOTAIR by RNA interference resulted in the loss of H3K27 trimethylation and EZH2 binding but increased interaction of RNA pol II with the GDF15 promoter region [41]. Transfection of HOTAIR siRNA affected invasiveness and apoptosis of Panc1 and L3.6pL cells, and inhibited the volume and weight growth of tumors in a murine xenograft model.

Lung cancer

In non-small cell lung cancers (NSCLCs), paired NSCLC tissues were detected higher HOTAIR expression than adjacent non-tumor ones. Overexpressed HOTAIR was associated with advanced pathological stage, lymph-node metastasis and shorter survival time. In addition, inhibiting HOTAIR expression increased the apoptosis and decreased the migration and invasion of NSCLC cells in vitro [78]. A similar result was reported recently by Nakagawa [79] and colleagues. Further study found that HOTAIR knockdown was associated with levels of matrix metalloproteinases (MMP2, MMP9) as well as expression of HOXA5. MMPs are involved in degrading the extracellular matrix (ECM). And HOXA5 is involved in NSCLC cell migration and invasion [80]. Another study by Zhuang [81] and co-workers found that, in the human lung adenocarcinoma cell line, HOTAIR was induced by Col-1 (type I collagen), a composition of interstitial extracellular matrix (ECM) which aberrantly increased in the tumor microenvironment. However, there was no significant quantitative correlation between HOTAIR and Col-1 in NSCLC cells, besides both overall upward trend. It is proposed the upregulation of HOXA5 and MMPs may be a carcinogenic mechanism of HOTAIR in Lung Cancer.

Laryngeal squamous cell carcinoma and nasopharyngeal carcinoma

In laryngeal squamous cell carcinomas (LSCCs) and nasopharyngeal carcinomas (NPCs), HOTAIR expression of tumor tissues was higher than adjacent nonneoplastic ones. HOTAIR expression levels were significantly associated with tumor size, clinical stage, lymph node and distant metastasis; and affected the overall survival and prognosis of cancer patients [82, 83]. HOTAIR knockdown inhibited the invasion of Hep-2 cells, and induced the apoptosis of Hep-2 cells. Moreover, study found cells with high invasive potential (5–8F, S18, CEN2) appeared higher expression levels of HOTAIR than cells with low invasive potential (6–10B, S26, CNE1). In a xenograft mice model, HOTAIR siRNA reduced the weight growth of LSCC. Promoter methylation analysis suggested

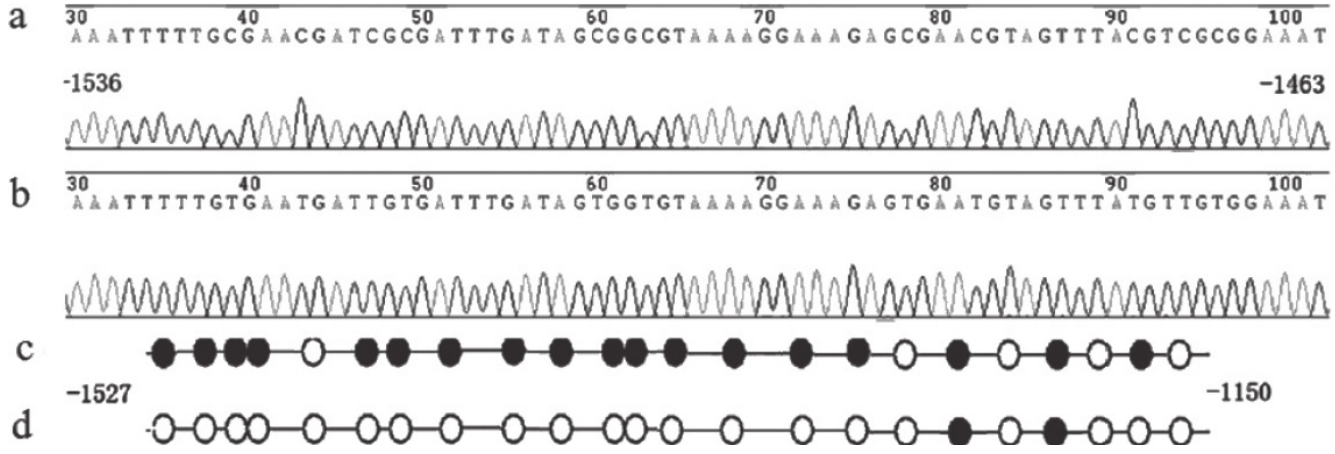

Figure 7. Methylation of the human PTEN promoter in Hep-2 cells.
(a) Representative results of bisulfite sequencing for control Hep-2 cells. (b) Hep-2 cells infected with HOTAIR siRNA lentivirus. (c) Methylation mapping of 23 CpG sites of the PTEN promoter region obtained from bisulfite sequencing in control Hep-2 cells. (d) Methylation mapping in Hep-2 cells infected with HOTAIR siRNA. Black circles, methylated; white circles, unmethylated (Figure modified from Ref 82).

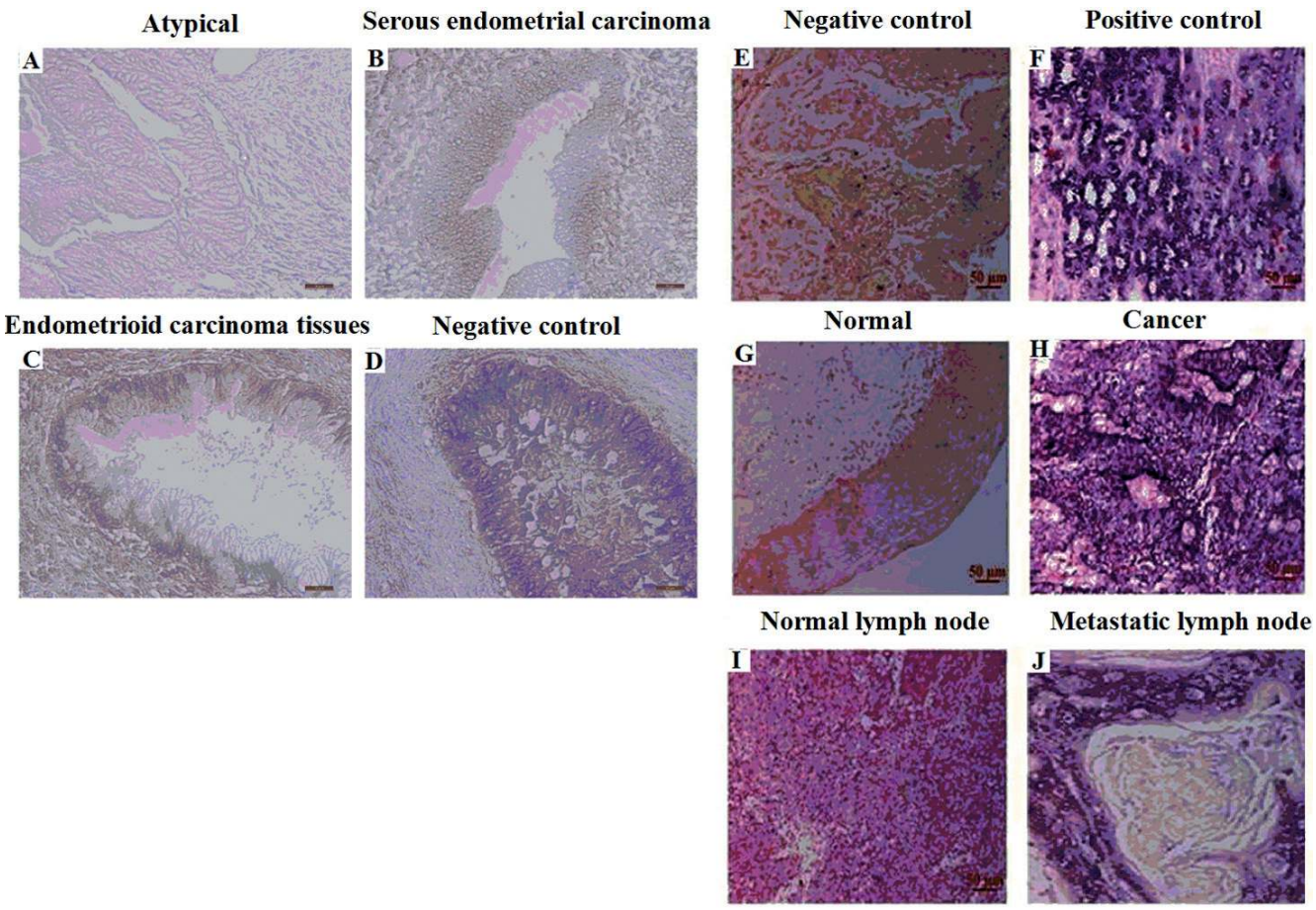

Figure 8. Representative images of in situ hybridization for HOTAIR in EC and ESCC.
Representative images of in situ hybridization for HOTAIR in normal endometrial (A), atypical (B), serous endometrial carcinoma (C) and endometrioid carcinoma tissues (D); in negative control (E), positive control (F), non-ESCC tissue (G), ESCC tissue (H), normal lymph node (I) and metastatic lymph node (J) (Figures modified from Ref 84 and 85).

that HOTAIR was involved in regulating PTEN methylation in Hep-2 cells Figure 7, which might be a potential oncogenic mechanism of HOTAIR in LSCC.

Esophageal squamous cell carcinoma and endometrial carcinoma

In situ hybridization revealed that HOTAIR expression in the tumor tissues was significantly upregulated compared with normal tissues in esophageal squamous cell carcinomas (ESCCs) and endometrial carcinomas (ECs) Figure 8. Kaplan–Meier and Cox regression analyses showed that expression level of HOTAIR was associated with the clinicopathologic parameters in ESCCs [84]. And a significant association between HOTAIR expression with the EC grade, lymph node metastasis and overall survival was observed in ECs [85]. In the formalin-fixed paraffin-embedded (FFPE) tissue, but not the frozen tissues, a higher HOTAIR expression appeared correlated with the depth of myometrial invasion and lymphovascular space invasion. Moreover, HOTAIR mediated the proliferation, colony formation and migratory capacity of ESCC cells in vitro. HOTAIR reprogrammed the gene expression profile of ESCC cells, including genes involved in cell migration and cell cycle. [86]. Silencing the expression of HOTAIR in ESCC cells could suppress the tumor growth in both size and weight in a mouse xenograft model [87].

Mesenchymal glioma

Zhang et al [88] analyzed the clinical significance and function of HOTAIR in glioma, and found that HOTAIR expression was closely related to glioma grade, prognosis and glioma molecular subtype. Multivariate Cox regression analysis revealed that HOTAIR was an independent prognostic factor

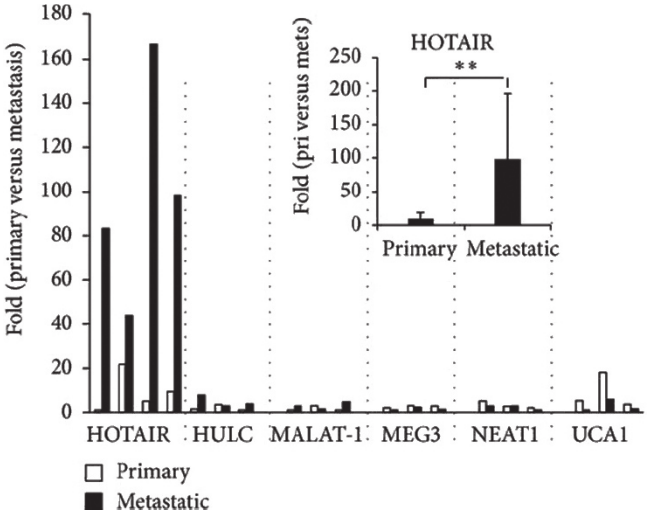

Figure 9. Expression profiles of lncRNAs in melanoma and matched lymph node metastatic tissues. Among the tested lncRNAs, HOTAIR was the most highly expressed in lymph node metastasis tissues of melanoma (Figure modified from Ref 89).

in glioblastoma multiforme patients. A gene set enrichment analysis between mesenchymal glioma patients with high and low HOTAIR expression showed that HOTAIR expression was associated with gene sets involved in cell cycle progression. In addition, HOTAIR reduction induced colony formation suppression, cell cycle G0/G1 arrest and orthotopic tumor growth inhibition. In summary, it was suggested that HOTAIR could serve as a prognostic factor for glioma patients, as well as a biomarker for identifying glioma molecular subtypes.

Melanoma

Tang et al [89] investigated the role of 6 metastasis-related lncRNAs (HOTAIR, HULC, MALAT1, MEG3, NEAT1 and UCA1) in 3 pairs of primary melanoma and matched lymph node metastatic tissues by qRT-PCR. Among the tested lncRNAs, HOTAIR was the most highly expressed in lymph node metastasis Figure 9. Knockdown of HOTAIR resulted in the reduction of motility and invasion of human melanoma cell line A375. In addition, HOTAIR knockdown suppressed the degradation of gelatin matrix, which was involved in tumor cell invasion. These data indicated that HOTIAR might be associated with the metastasis of melanoma.

Conclusion and future perspectives

In summary, with HOTAIR becomes a hot topic, more and more studies about the relevance of HOTAIR with cancers have been reported. It has been demonstrated that anomalous expression of HOTAIR appeared associated with a wide range of cancer characteristics, such as apoptosis, proliferation and invasiveness of tumor cells; and HOTAIR expression affected the survival and prognosis of cancer patients. The molecular mechanisms of HOTAIR in cancer progression involve in recruiting PRC2 and LSD1 complexes, H3K27 methylation and H3K4 demethylation, and ultimately gene silencing. However, the precise mechanism of how dysregulated HOTAIR expressions drive cancer progression is not yet fully understood. It is also unclear whether other components of PRC2 and LSD1 complexes affect their interactions with HOTAIR; whether HOTAIR interacts with additional chromatin-modifying enzymes through other molecular mechanisms; Furthermore, whether HOTAIR could be a molecular mark for diagnosis or prognosis of cancers and serve as a therapeutic target to cancer progression. All of these require further investigation.

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