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Review

The molecular mechanism of HOTAIR in tumorigenesis, metastasis, and drug resistance

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Long non-coding RNAs have been reported to play an important role in cellular metabolism and development. Homeobox transcript antisense intergenic RNA (HOTAIR), a long non-coding RNA, is pervasively over-expressed in most human cancers compared with non-cancerous adjacent tissues. Although many articles have reported that HOTAIR is closely associated with metastasis, epithelial-mesenchymal transition, advanced pathological stage, drug resistance, and poor prognosis, the role of HOTAIR in gene regulation and tumor development is largely unknown, and the potential molecular mechanisms are not completely clear yet. In this review, we summarized the recent progress in the study of the major functions of HOTAIR. miR-331-3p, miR-130a, miR-7, miR-141, HER2, c-MYC, WIF-1, RBM38, PTEN, and Col-1 are involved in the HOTAIR regulation network. We tried to elucidate the molecular mechanisms of HOTAIR in the aspects of tumorigenesis, metastasis, drug resistance, and regulation.

Keywords cancer; lncRNA; HOTAIR; metastasis; EMT; drug resistance

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Introduction

Long non-coding RNAs (lncRNAs) are non-protein coding transcripts ranging from 200 bases to about 100 kb bases long, whereas miRNAs are evolutionarily conserved 20–24 nucleotide long single stranded RNAs involved in post-transcriptional gene silencing. Homeobox transcript antisense intergenic RNA (HOTAIR), a lncRNA which is up-regulated in human tumors and cancers, such as breast cancer, liver cancer, ovarian cancer, gastric cancer, pancreatic cancer, glioma and non-small cell lung cancer (NSCLC), is a 2158 nucleotide lncRNA. It is located on chromosome 12q13.13, which is a regulatory boundary in the homeobox C cluster.

Previous studies have shown that HOTAIR is a powerful predictor of metastasis and drug resistance, and is associated with epithelial-mesenchymal transition (EMT) [1]. One meta-analysis has demonstrated that HOTAIR is an independent prognostic factor for cancer metastasis, and is associated with larger tumor size, poor overall survival, and advanced pathological stage [2]. Other studies have reported that HOTAIR is associated with drug resistance, cellular proliferation, invasiveness, and clinical relapse [3]. Knockdown of HOTAIR reduces the motility and invasion of human melanoma cell line A375 [4], inhibits the proliferation and invasion of endometrial carcinoma cells both *in vitro* and *in vivo*, suppresses tumor invasion, and reverses EMT in gastric cancer cells [5].

Although the significance of HOTAIR has been discovered, the underlying molecular mechanisms and regulation network remain largely unknown. Zhang *et al*. [6] have reported that HOTAIR interacts with polycomb repressive complex 2 (PRC2) and regulates chromosome occupancy by EZH2 (a subunit of PRC2), which leads to histone H3 lysine 27 (H3K27) trimethylation of the homeobox D locus, enforcing a silent chromatin state at Hox and additional genes which contribute to cancer development and metastasis. But why HOTAIR is associated with the invasion, metastasis, EMT, and drug resistance remains poorly understood [7].

In this review, we discussed the newly discovered molecular mechanism of HOTAIR, with a focus on tumorigenesis, metastasis (including migration and invasion, EMT), drug resistance, and regulation of HOTAIR.

Molecular Mechanisms of HOTAIR

It is apparent that lncRNA may affect the cellular mechanisms in many ways [8]. However, HOTAIR is only found to be involved in some mechanisms, for example, cooperation with chromatin modifying enzymes to promote epigenetic activation or silencing gene expression [9], and function as a miRNA sponge or an inducer of ubiquitin-mediated proteolysis. Here, we reviewed the molecular mechanisms of HOTAIR in the following categories.

Tumorigenesis

One study has reported that the oncogenic role of HOTAIR in human laryngeal squamous cell cancer is to promote

phosphatase and tensin homolog (PTEN) methylation [10]. PTEN acts as a tumor repressor via inactivating PI3K/p-AKT/p-MDM2/p53 [11] and PI3K/AKT/mTOR [12] signaling pathways. Activation of PI3K-AKT-mTOR1 signaling pathway results in the proliferation, survival, apoptosis, cell cycle, metabolism, and angiogenesis [13,14]. Methylation of PTEN results in the down-regulation of PTEN at mRNA and protein levels. Loss of PTEN results in the repression of p53-mediated apoptosis and chronic activation of PI3K-AKT-mTOR1 signaling. As a consequence, over-expression of HOTAIR leads to tumorigenesis. On the other hand, suppressed expression of HOTAIR inhibits the proliferation and tumourigenesis both *in vitro* and *in vivo* [15,16].

Migration and invasion

Previous studies have shown that HOTAIR promotes tumor metastasis. *In vitro* assays showed that the suppression of HOTAIR expression in highly metastatic epithelial ovarian cancer cell lines significantly reduced cell migration/invasion [17], which was partially mediated by the regulation of certain matrix metalloproteinases. In small-cell lung cancer cell lines, knockdown of HOTAIR in SBC-3 cells led to decreased proliferation activity and decreased invasiveness *in vitro* [3]. Gene expression analysis indicated that the depletion of HOTAIR resulted in up-regulation of cell adhesion-related genes such as *astrotactin1* (*ASTN1*), *protocadherin-alpha* (*PCDHA1*), and mucin production-related genes such as *mucin 5AC* (*MUC5AC*).

To study the molecular mechanism of HOTAIR knockdown, another group profiled its gene expression pattern in hepatocellular carcinoma (HCC) cells by microarray analysis [18]. Overall, 296 genes were found to be differentially expressed in HOTAIR knockdown cells. After bioinformatics analysis, the up-regulation of QKI, CD82, and RNA binding motif protein 38 (RBM38) was validated after knockdown of HOTAIR. Their results suggested that these genes have little effect on HCC cell proliferation. Furthermore, it was also found that the relative mRNA level of *RBM38* was significantly down-regulated in HCC tissues. RBM38 knockdown promoted the migration and invasion in HCC cells. But the role of RBM38 in cell migration and invasion is still unclear.

Epithelial-mesenchymal transition

Recently, HOTAIR was reported to function as a competing endogenous RNA to regulate v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 2 (HER2) expression by sponging miR-331-3p in gastric cancer [19]. HER2 is a target of miR-331-3p. The repression of miR-331-3p resulted in the up-regulation of HER2 expression. HER2 over-expression resulted in EMT [20], which was accompanied by increased expression of a known EMT regulator Slug. These authors further investigated how HER2 induced Slug expression, and found, for the first time, that HER2 activation resulted in concurrent phosphorylation of AKT and heat shock factor-1 (HSF-1). AKT directly interacted with HSF-1 and phosphorylated HSF-1 at S326. Furthermore, there are four consensus HSF sequence-binding elements, the binding sites for HSF-1, located in the Slug promoter. In conclusion, HOTAIR could promote EMT via HER2/AKT/HSF-1/Slug pathway by inhibiting miR-331-3p.

Moreover, HOTAIR was reported to inhibit Wnt inhibitory factor 1 (WIF-1) expression and activate Wnt pathway [21]. WIF-1 plays an important role in Wnt/beta-catenin signaling pathway. Inverse correlation between HOTAIR and WIF-1 expression was demonstrated both in esophageal squamous cell carcinoma cells and tissues. Mechanistically, HOTAIR directly decreases WIF-1 expression by promoting its histone H3K27 methylation in the promoter region and then activates the Wnt/beta-catenin signaling pathway. Activation of the Wnt/beta-catenin signaling pathway promotes EMT by decreasing the level of miR-200a [22,23]. The relationship between miR-200a and HOTAIR has not been reported yet.

In addition, HOTAIR was reported to promote EMT by reducing the expression of miR-7, which might be mediated by inhibiting the HoxD10 expression [24]. It was found that over-expression of miR-7 partially reversed EMT by targeting SET domain bifurcated 1 (SETDB1) in MDA-MB-231 cells. SETDB1 is an enzyme that methylates histone H3 lysine 9 (H3K9), and positively maintains the state of stem cells. It was demonstrated that miR-7 could inhibit the EMT-dependent metastasis of breast cancer cells and breast cancer stem cells by inhibiting SETDB1 and the STAT3 signal pathway. The results of CHIP-PCR assay suggested that STAT3 could bind the promoters of c-MYC and Twist, and could promote their expression. It was reported that the c-MYC could accelerate the expression of miR-9, which decreased the E-cadherin expression by recognizing its 3′UTR [25], and that Twist could directly inhibit the E-cadherin expression by directly binding to the E-box on its promoter.

Drug resistance

HOTAIR was found to contribute to cisplatin resistance of human lung adenocarcinoma cells via down-regulation of $p21^{WAF1/CIP1}$ expression [26]. The $p21^{WAF1/CIP1}$ is a well-known cyclin-dependent kinase inhibitor induced by various stress stimuli. There was a growing body of evidence suggesting that functional loss of p21 or p27 can mediate a drug-resistance phenotype [27]. HOTAIR is significantly down-regulated in cisplatin-responding lung adenocarcinoma tissues, and its expression is inversely correlated with *p21* mRNA expression, suggesting that HOTAIR may contribute to the cisplatin resistance, at least in part, through the regulation of p21 expression.

Regulation of HOTAIR

It was reported that the significant enrichment of both NF-κB and c-MYC on the HOTAIR promoter was observed using ChIP assay, and resulted in 16-fold induction of HOTAIR when treated with tumor necrosis factor-α [28]. It was also hypothesized that HORAIR inhibited IκBα (an inhibitor of NF-κB), and then activated c-MYC expression, which in turn induced HOTAIR expression through SETDB1/STAT3 signaling pathway [24]. It was also believed that this novel pathway may be involved in cisplatin-resistant ovarian cancer, which is currently under intensive investigation.

Another group demonstrated that HOTAIR was transcriptionally induced by estradiol (E2), bisphenol-A (BPA), and diethylstilbestrol (DES) in breast cancer cells [7,29]. Its promoter contains multiple functional estrogen response elements. Estrogen receptors (ERs), ER co-regulators such as mixed lineage leukemia 1 (MLL1) and MLL3, and CREB-binding protein/p300 bind to the HOTAIR promoter in the presence of estradiol, BPA, and DES. Therefore, the transcription of HOTAIR is up-regulated.

HOTAIR also was reported to be down-regulated by miR-141 in human cancer cells [30]. Immunoprecipitation results showed that HOTAIR was pulled down together with miR-141 in the Argonaute2 (Ago2) complex. miR-141 significantly decreased HOTAIR expression to 5% of the control levels, whereas miR-141 reduced HOTAIR expression to only 60%−70% compared with controls when Ago2 was knocked down. Therefore, miR-141 bound to HOTAIR in a sequence-specific manner and suppressed HOTAIR expression. Since miR-141 did not have significant effect on luciferase activity using a HOTAIR promoter, the authors proposed that miR-141 could not transcriptionally repress HOTAIR.

In addition, HOTAIR was reported to be induced by type I collagen (Col-1) in lung cancer cells [31]. Col-1, a component of extracellular matrix, is aberrantly enriched in the tumor microenvironment and promotes tumor progression. HOTAIR and Col-1 are concurrently up-regulated in human NSCLCs. In consistent with this finding, Col-1 was found to activate the expression of a reporter gene controlled by the human HOTAIR promoter. And the induction of HOTAIR by Col-1 was diminished by a neutralizing antibody against the Col-1 receptor alpha 2 beta 1 integrin. These findings indicated that tumor-promoting Col-1 could up-regulate the expression of HOTAIR in NSCLC cells.

Osteopontin (OPN), a secreted phosphoglycoprotein, was reported to increase cell migration via EGFR and MET [32,33]. Most recently, OPN was found to induce the expression

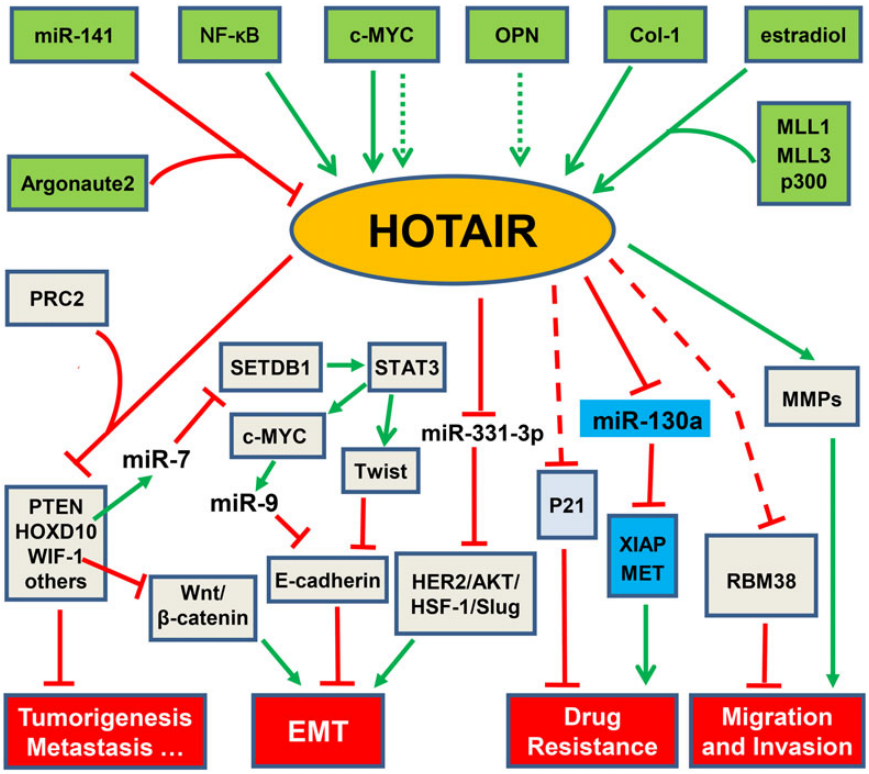

Figure 1. Schematic illustration of HOTAIR regulation network HOTAIR can be induced by c-MYC directly or indirectly through SETDB1/STAT3 signaling pathway. Osteopontin (OPN) can suppress IRF1 by up-regulating the PI3K/AKT pathway via CD44 and finally increase the expression of HOTAIR. Epigenetic regulation by HOTAIR and PRC2 can silence many genes and result in tumorigenesis, metastasis, and other undiscovered functions. The molecular mechanisms of HOTAIR in down-regulating p21 and RBM38 remain unclear, so these pathways were depicted with red dotted lines.

of HOTAIR in a time- and dose-dependent manner [34]. By up-regulating the PI3K/AKT pathway via CD44, OPN decreased interferon regulatory factor-1 (IRF1) expression and further elevated the level of HOTAIR. In support of this notion, the authors found that IRF1 could bind to the HOTAIR promoter region and decrease its transcriptional activity through chromatin immunoprecipitation and luciferase activity assays.

Perspective

HOTAIR was reported to have significant influence on the proliferation, metastasis, EMT, and drug resistance in various human cancers. We discussed the mechanisms of HOTAIR in these biological processes, involving methylation, miR-331-3p, miR-7, miR-141, HER2, c-MYC, WIF-1, RBM38, PTEN, and Col-1. We also summarized how HOTAIR was regulated and which pathway was involved in the induction of HOTAIR (**Fig. 1**). Moreover, since HOTAIR regulates the expression of hundreds of genes [18], the understanding of HOTAIR remains poor. Further investigation is necessary to discover other roles played by HOTAIR. For example, HOTAIR level is highly up-regulated in senescent cells, causing rapid decay of targets Ataxin-1 and Snurportin-1 [35]. This observation uncovered a role for HOTAIR, as a platform for protein ubiquitination.

In addition, HOTAIR may contribute to drug resistance through regulation of miR-130a. It has been reported that a positive correlation between *c-MYC* and *HOTAIR* mRNA level is observed in 65 matched pairs of gall bladder cancer tissues, accompanied by a negative regulation of miR-130a [36]. It was demonstrated that HOTAIR would be a direct target of c-MYC through interaction with putative c-MYC target response element in the upstream region of HOTAIR. It was also predicted that HOTAIR may harbor a miR-130a binding site which is vital for the regulation of miR-130a. The c-MYC is associated with the regulation of HOTAIR, while miR-130a is associated with drug resistance.

For example, it was reported that the down-regulation of miR-130a contributed to cisplatin resistance in ovarian cancer cells by directly targeting X-linked inhibitor of apoptosis [37]. This finding suggested that miR-130a might play a role in the development of cisplatin resistance. In contrast, overexpression of miR-130a was found to overcome gefitinib resistance by targeting MET (also called c-Met or hepatocyte growth factor receptor) in NSCLC cell lines [38]. It was also demonstrated that miR-130a could bind to the 3′-UTR of MET and significantly suppress its expression. The expression of MET was associated with both primary and acquired resistance to gefitinib.

Moreover, drug resistance is a major obstacle in cancer chemotherapy. In order to overcome drug resistance, more efforts should be made to investigate the molecular mechanisms of HOTAIR in drug resistance, which will provide useful information to rational personal anti-cancer therapy or new drug design and screening.

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