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An Overview on Long non coding RNA HOTAIR

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Abstract:

HOX Transcript Antisense Intergenic RNA (HOTAIR) is a long non-coding RNA (lncRNA) located on chromosome 12q13.13, transcribed from the HOXC locus. Despite not encoding proteins, HOTAIR plays a critical regulatory role in epigenetic gene silencing. It functions as a molecular scaffold that recruits chromatin-modifying complexes, particularly Polycomb Repressive Complex 2 (PRC2) and LSD1/CoREST/REST, to target genomic regions such as the HOXD cluster, leading to H3K27 trimethylation and H3K4 demethylation, respectively. Through these epigenetic modifications, HOTAIR influences cellular processes such as cell differentiation, proliferation, migration, and invasion. Dysregulation of HOTAIR expression has been strongly associated with tumor progression, epithelial-mesenchymal transition (EMT), drug resistance, and poor prognosis in several cancers including breast, colorectal, liver, gastric, and lung cancers. Due to its tissue-specific expression, stability in blood and exosomes, and strong correlation with tumor aggressiveness, HOTAIR is considered a promising biomarker for diagnosis, prognosis, and a potential therapeutic target in cancer.

Keywords: HOTAIR; Long non-coding RNA; Epigenetic regulation; Polycomb Repressive Complex 2 (PRC2); LSD1; Chromatin remodeling; Gene silencing; Epithelial-mesenchymal transition (EMT); Cancer progression; Biomarkers; Drug resistance.

Introduction:

A varied class of RNA transcripts longer than 200 nucleotides, long non-coding RNAs (lncRNAs) do not encode proteins but are essential for transcriptional, post-transcriptional, and epigenetic regulation. More and more data indicates that lncRNAs play a crucial role in regulating gene expression and are implicated in vital biological functions such cell division, growth, and death. Because of its enormous influence on transcriptional gene silencing and chromatin remodeling, HOX Transcript Antisense Intergenic RNA (HOTAIR) has become one of the most functionally significant lncRNAs (1).

HOTAIR mainly serves as an epigenetic scaffold and is transcribed from the HOXC locus on chromosome 12q13.13. In order to suppress target genes by histone modification, it attracts several chromatin-modifying complexes to particular genomic areas, most notably the Polycomb Repressive Complex 2 (PRC2) and the LSD1/CoREST/REST complex (2). HOTAIR plays a role in transcriptional reprogramming that modifies cellular identity and behavior by promoting H3K27 trimethylation and H3K4 demethylation. This reprogramming affects pathways linked to invasion, metastasis, and proliferation.

The onset and spread of cancer have been closely associated with the dysregulation of HOTAIR expression. A number of cancers, including breast, colorectal, gastric, hepatic, and lung tumors, have been shown to overexpress HOTAIR, which increases the risk of metastasis, promotes the epithelial-mesenchymal transition (EMT), and increases resistance to treatment (3). HOTAIR is presently being investigated as a predictive biomarker and a

therapeutic target in the management of cancer because of its important involvement in tumor aggressiveness and its detectability in tissues and circulating exosomes.

Definition and Location:

The 2,158 bp long non-coding RNA (lncRNA) known as HOX transcript antisense RNA (HOTAIR) has six exons and is situated between the HOXC11 and HOXC12 genes on chromosome 12q13.13. Numerous transcription factors, such as AP1, Sp1, ERE elements, HRE elements, and NF-kB, have binding sites in its promoter region. In order to control chromatin shape and enable transcriptional silencing, HOTAIR is essential (4).

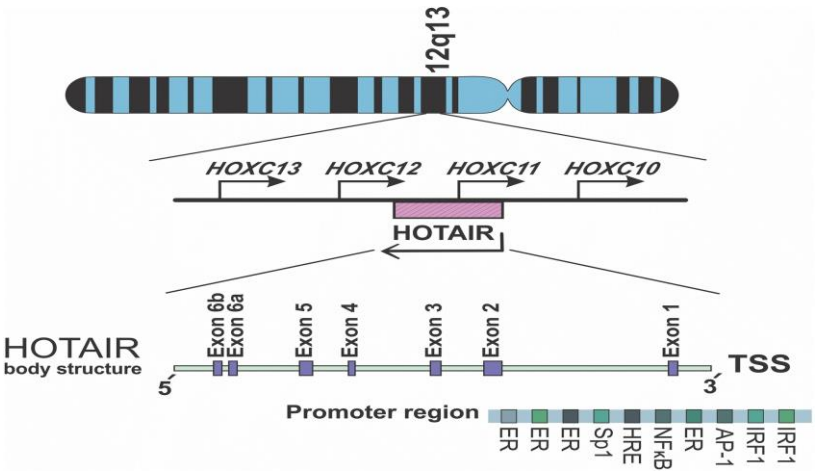

Figure 1: Location of LNC RNA HOTAIR.(5)

Function:

Early studies showed that HOTAIR attaches to the 5′ end of the Polycomb repressive complex 2 (PRC2), which helps to preserve cell stemness and block cell differentiation by suppressing genes linked to differentiation through H3K27 histone trimethylation. Furthermore, lysine-specific histone demethylase 1A (LSD1), another important chromatin modification implicated in gene silencing, interacts with HOTAIR at its 3′ terminus. By activating the RE1-silencing transcription factor (REST) and CoREST, two proteins crucial to transcriptional repression, LSD1 creates a multiprotein complex. (4)

The PRC2 and LSD1 complexes interact more easily thanks to the molecular scaffolding provided by HOX transcript antisense RNA (HOTAIR). Through H3K27 trimethylation (mediated by PRC2) and H3K4 demethylation (mediated by LSD1), the HOTAIR-PRC2-LSD1 complex suppresses transcription and causes epigenetic changes that aid in targeted gene silencing. This complex, for example, can be targeted to the 5′ end of the HOXD locus on chromosome 2, where it methylates and demethylates H3K27 and H3K4 to mute genes implicated in metastasis suppression (6).

Both post-transcriptional and post-translational levels of gene expression can be controlled by HOX transcript antisense RNA (HOTAIR). Post-transcriptionally, it interacts with splicing factors to modify splicing and base pairs with translation factors or ribosomes to influence translation. It has been documented that HOTAIR serves as a platform for protein ubiquitination at the post-translational level, enabling the eventual destruction of those proteins (6).

MiRNA recognition elements (MREs) are found in most lncRNAs, suggesting that lncRNAs can control the transcription of certain miRNAs and contribute to their synthesis, maturation, and destruction. Numerous investigations have shown that HOTAIR and microRNAs interact, and that these interactions have an impact on a number of cellular functions (7).

By promoting PRC2's recruitment to its target HOXD genes and repressing them, HOTAIR plays a critical role in the formation of the lumbosacral region throughout embryogenesis (6).

Furthermore, HOTAIR has been linked to cell cycle regulation in a number of investigations. By modifying the Rb-E2F signaling pathway and the CDK4/6-cyclin D complex, it encourages cell cycle advancement past the G1 phase restriction point (8).

Role of LncRNA HOTAIR in cancer:

The majority of solid tumors have shown aberrant HOTAIR expression in the last ten years, highlighting the protein's critical function in controlling tumor start, development, angiogenesis, progression, recurrence, treatment resistance, and poor prognosis (9)

Because HOTAIR overexpression binds to the androgen receptor (AR) protein and inhibits its degradation, it promotes the proliferation and invasion of prostate cancer cells in urological malignancies. HOTAIR contributes to doxorubicin chemosensitivity and acts as an independent prognostic marker for tumor recurrence in bladder cancer. Additionally, people with bladder cancer may have it in their urine. (6)

The International Federation of Gynecology and Obstetrics (FIGO) stage, tumor histological grade, lymph node metastases, and poor survival outcomes are all linked to HOTAIR's upregulation in epithelial ovarian cancer tissues in gynecological cancers. Its expression in cervical carcinoma is associated with prognosis, lymph node metastases, and clinical-pathological features (6). Additionally, HOTAIR influences the growth and proliferation of cervical cancer cells via interacting with different mRNAs. Additionally, in patients with cervical cancer, high levels of HOTAIR in the blood are closely associated with lymph node metastases, advanced disease, and a bad prognosis. (10). Abnormal HOTAIR expression in endometrial cancer is linked to poor prognosis, lymph node metastasis, tumor grade, and the emergence of cisplatin resistance.

A noteworthy biomarker of colorectal and gastric malignancies, HOTAIR overexpression is strongly associated with tumor stage, lymph node involvement, distant metastases, and decreased survival rates in gastrointestinal cancers (11). HOTAIR has been found in patient plasma in gastric cancer, and its levels in the blood can be used to determine which patients will benefit from combination therapy with fluorouracil and platinum (12). HOTAIR is significantly expressed in liver cancer and is closely associated with both tumor progression and clinical-pathological characteristics. Additionally, in patients with hepatocellular carcinoma, HOTAIR silencing increases treatment sensitivity to doxorubicin and cisplatin (13)

In oral malignancies, HOTAIR overexpression has been linked to histological grade and stage in laryngeal squamous cell carcinoma (LSCC). Furthermore, HOTAIR contributes to the modulation of cisplatin sensitivity in LSCC cells (14).

A poor prognosis, lymph node metastases, and advanced stages of lung cancer are all associated with abnormal HOTAIR expression. In individuals with non-small cell lung cancer (NSCLC), there is also a clear correlation between high HOTAIR expression and cisplatin resistance. Additionally, circulating HOTAIR has been found in the plasma of patients with lung cancer, where it is linked to clinical-pathological characteristics (15, 16).

Role of long noncoding RNA in colorectal cancer:

In terms of incidence and fatality rates, colorectal cancer (CRC) is one of the three most common and deadly malignancies. In patients with colorectal cancer, elevated HOTAIR is closely associated with greater tumor infiltration, venous invasion, distant metastases, and worse overall survival (17). Furthermore, as liver metastasis is a major cause of cancer-related fatalities in colorectal cancer, elevated HOTAIR expression has been proposed as a possible prognostic biomarker for poor survival outcomes (18). Furthermore, HOTAIR has been linked to a possible mechanism that influences bacterial activity and drives colorectal carcinogenesis and development (19). Another study showed that miR-203a-3p negatively affects HOTAIR expression in colorectal cancer cell lines and that HOTAIR levels were elevated in colorectal cancer tissues. According to functional tests, colorectal cancer cell proliferation and chemotherapy resistance are reduced when HOTAIR is silenced or miR-203a-3p expression is increased (20).

References:

1. Statello, L., Guo, C. J., Chen, L. L., & Huarte, M. (2021). Gene regulation by long non-coding RNAs and its biological functions. Nature Reviews Molecular Cell Biology, 22(2), 96–118. https://doi.org/10.1038/s41580-020-00315-9
2. Geisler, S., & Coller, J. (2013). RNA in unexpected places: Long non-coding RNA functions in diverse cellular contexts. *Nature Reviews Molecular Cell Biology, 14*(11), 699–712. https://doi.org/10.1038/nrm3679
3. Xue, X., Yang, Y. A., Zhang, A., Fong, K. W., Kim, J., Song, B., et al. (2016). LncRNA HOTAIR enhances ER signaling and confers tamoxifen resistance in breast cancer. Oncogene, 35(21), 2746–2755. https://doi.org/10.1038/onc.2015.340
4. Majello, B., Gorini, F., Saccà, C. D., & Amente, S. (2019). Expanding the role of the histone lysine-specific demethylase lsd1 in cancer. *Cancers*, *11*(3). https://doi.org/10.3390/cancers11030324
5. Mozdarani, H., Ezzatizadeh, V., & Rahbar Parvaneh, R. (2020). The emerging role of the long non-coding RNA HOTAIR in breast cancer development and treatment. In *Journal of Translational Medicine* (Vol. 18, Issue 1). BioMed Central Ltd. https://doi.org/10.1186/s12967-020-02320-0
6. Cantile, M., Di Bonito, M., Cerrone, M., Collina, F., De Laurentiis, M., & Botti, G. (2020). Long non-coding rna hotair in breast cancer therapy. In *Cancers* (Vol. 12, Issue 5). MDPI AG. https://doi.org/10.3390/cancers12051197
7. Han, B., Peng, X., Cheng, D., Zhu, Y., Du, J., Li, J., & Yu, X. (2019). Delphinidin suppresses breast carcinogenesis through the HOTAIR/microRNA-34a axis. *Cancer Science*, *110*(10), 3089–3097. https://doi.org/10.1111/cas.14133
8. Liu, M., Zhang, H., Li, Y., Wang, R., Li, Y., Zhang, H., Ren, D., Liu, H., Kang, C., & Chen, J. (2018). HOTAIR, a long noncoding RNA, is a marker of abnormal cell cycle regulation in lung cancer. *Cancer Science*, *109*(9), 2717–2733. https://doi.org/10.1111/cas.13745
9. Xu, S., Kong, D., Chen, Q., Ping, Y., & Pang, D. (2017). Oncogenic long noncoding RNA landscape in breast cancer. *Molecular Cancer*, *16*(1). https://doi.org/10.1186/s12943-017-0696-6
10. Liu, M., Jia, J., Wang, X., Liu, Y., Wang, C., & Fan, R. (2018). Long non-coding RNA HOTAIR promotes cervical cancer progression through regulating BCL2 via targeting miR-143-3p. *Cancer Biology and Therapy*, *19*(5), 391–399. https://doi.org/10.1080/15384047.2018.1423921
11. Luo, Z. F., Zhao, D., Li, X. Q., Cui, Y. X., Ma, N., Lu, C. X., Liu, M. Y., & Zhou, Y. (2016). Clinical significance of HOTAIR expression in colon cancer. *World Journal of Gastroenterology*, *22*(22), 5254–5259. https://doi.org/10.3748/wjg.v22.i22.5254
12. Zhao, W., Dong, S., Duan, B., Chen, P., Shi, L., Gao, H., & Qi, H. (2015). Original Article HOTAIR is a predictive and prognostic biomarker for patients with advanced gastric adenocarcinoma receiving fluorouracil and platinum combination chemotherapy. In *Am J Transl Res* (Vol. 7, Issue 7). www.ajtr.org
13. Ishibashi, M., Kogo, R., Shibata, K., Sawada, G., Takahashi, Y., Kurashige, J., Akiyoshi, S., Sasaki, S., Iwaya, T., Sudo, T., Sugimachi, K., Mimori, K., Wakabayashi, G., & Mori, M. (2013). Clinical significance of the expression of long non-coding RNA HOTAIR in primary hepatocellular carcinoma. *Oncology Reports*, *29*(3), 946–950. https://doi.org/10.3892/or.2012.2219
14. Li, D., Feng, J., Wu, T., Wang, Y., Sun, Y., Ren, J., & Liu, M. (2013). Long intergenic noncoding RNA HOTAIR is overexpressed and regulates PTEN methylation in laryngeal squamous cell carcinoma. *American Journal of Pathology*, *182*(1), 64–70. https://doi.org/10.1016/j.ajpath.2012.08.042
15. Liu, M. Y., Li, X. Q., Gao, T. H., Cui, Y., Ma, N., Zhou, Y., & Zhang, G. J. (2016). Elevated HOTAIR expression associated with cisplatin resistance in non-small cell lung cancer patients. *Journal of Thoracic Disease*, *8*(11), 3314–3322. https://doi.org/10.21037/jtd.2016.11.75
16. Li, N., Wang, Y., Liu, X., Luo, P., Jing, W., Zhu, M., & Tu, J. (2017). Identification of Circulating Long Noncoding RNA HOTAIR as a Novel Biomarker for Diagnosis and Monitoring of Non–Small Cell

Lung Cancer. *Technology in Cancer Research and Treatment*, *16*(6), 1060–1066. https://doi.org/10.1177/1533034617723754

17. Chen, S., Zhang, C., & Feng, M. (2020). Prognostic value of lncRNA HOTAIR in colorectal cancer: A meta-analysis. *Open Medicine (Poland)*, *15*(1), 76–83. https://doi.org/10.1515/med-2020-0012
18. Liu, F., Song, Z. M., Wang, X. Di, Du, S. Y., Peng, N., Zhou, J. R., & Zhang, M. G. (2021). Long Non-coding RNA Signature for Liver Metastasis of Colorectal Cancers. *Frontiers in Cell and Developmental Biology*, *9*. https://doi.org/10.3389/fcell.2021.707115
19. Tan, X., Mao, L., Huang, C., Yang, W., Guo, J., Chen, Z., & Chen, Z. (2021). Comprehensive analysis of lncRNA-miRNA-mRNA regulatory networks for microbiota-mediated colorectal cancer associated with immune cell infiltration. *Bioengineered*, *12*(1), 3410–3425. https://doi.org/10.1080/21655979.2021.1940614
20. Xiao, Z., Qu, Z., Chen, Z., Fang, Z., Zhou, K., Huang, Z., Guo, X., & Zhang, Y. (2018). LncRNA HOTAIR is a Prognostic Biomarker for the Proliferation and Chemoresistance of Colorectal Cancer via MiR-203a-3p-Mediated Wnt/ß-Catenin Signaling Pathway. *Cellular Physiology and Biochemistry*, *46*(3), 1275–1285. https://doi.org/10.1159/000489110