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REVIEW

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HOTAIR in cancer: diagnostic, prognostic, and therapeutic perspectives

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Abstract

The long non-coding RNA *HOTAIR* is overexpressed in many cancers and is associated with several cancer-promoting effects, including increased cell proliferation, migration and treatment resistance. *HOTAIR* levels correlate with tumor stage, lymph node metastasis and overall survival in patients with various types of cancer. This highlights the potential uses of *HOTAIR*, including early cancer detection, predicting patient outcome, identifying high-risk individuals and assisting in therapy selection and monitoring. The aim of this review is to provide a comprehensive summary of the research progress, molecular mechanisms and clinical significance of *HOTAIR* in various human cancers. In addition, the clinical applications of *HOTAIR*, such as targeted therapy, radiotherapy, chemotherapy and immunotherapy, are discussed, and relevant information on the potential future advances of *HOTAIR* in cancer research is provided.

Keywords Cancer, *HOTAIR*, Biomarker, Chemotherapy, Immunotherapy, Radiotherapy

Introduction

It is estimated that non-coding RNAs (ncRNAs) comprise more than 90% of the human genome [1]. These ncRNAs have been recognized as central regulators of vital biological functions, which has made them the subject of considerable scientific attention and scrutiny [2]. Long non-coding RNAs, or LncRNAs, are RNA molecules that contain about 200 nucleotides but do not encode proteins. There is growing evidence demonstrates the dysregulation of lncRNAs in tumors [3]. Numerous cellular biological processes, including cell cycle progression, chromatin remodeling, invasion, metastasis, apoptosis, gene transcription, and post-transcriptional processing, are regulated by lncRNAs.

A well-studied long non-coding RNA, the Hox transcript antisense intergenic RNA or *HOTAIR*, is located on chromosome 12q13 within the HOXC gene cluster, surrounded by the *HOXC11* and *HOXC12* genes [4]. *HOTAIR*, the first discovered LncRNA with retrotranspositional properties, can be detected in various tumor types. Gupta et al. were the first to demonstrate the oncogenic properties of *HOTAIR* in breast cancer. Their results showed that *HOTAIR* significantly increased in both primary and metastatic breast cancer by facilitating the methylation of histone H3 lysine 27 in a PRC2-dependent manner. This increase was critical in promoting breast cancer cell invasion and proliferation [4]. Recent studies have shown that *HOTAIR* acts as a critical mediator of chromatin state and is involved in promoting transcriptional silencing [5]. There is a negative correlation with tumor development and patient

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prognosis in several malignancies, including colon, breast, liver and gastric cancer. It is frequently overexpressed in a number of primary and metastatic cancers. It is a valuable biomarker for the assessment of clinicopathological features and prognosis of cancer patients as it correlates strongly with tumor size, stage and clinical outcome. In addition, *HOTAIR* can influence tumor cell proliferation, apoptosis, invasion and metastasis, further highlighting its role in promoting cancer progression [6].

Functions and molecular mechanisms of HOTAIR

HOTAIR is a crucial epigenetic regulator that contributes to the regulation of transcriptional silencing and the chromatin state of genes. Previous studies have shown that HOTAIR's mechanisms of action depend on interactions with protein or RNA partners; four key molecules associated with *HOTAIR* function have already been investigated [7]. The molecular mechanisms and functions of *HOTAIR* are depicted in Fig. 1.

Most research has focused on Polycomb repression complex 2 (*PRC2*), which uses trimethylation of histone H3 Lys 27 (H3K27me3) to signal a gene for transcriptional repression [8, 9]. EZH2, EED, SUZ12 and RbAp46/48 are the four major components of the PRC2 complex [10]. Although EZH2 plays a crucial role in the methyltransferase process, its catalytic activity relies equally on its three subunits [11]. Previous research has shown that *HOTAIR* can bind to PRC2 using an 89 bp

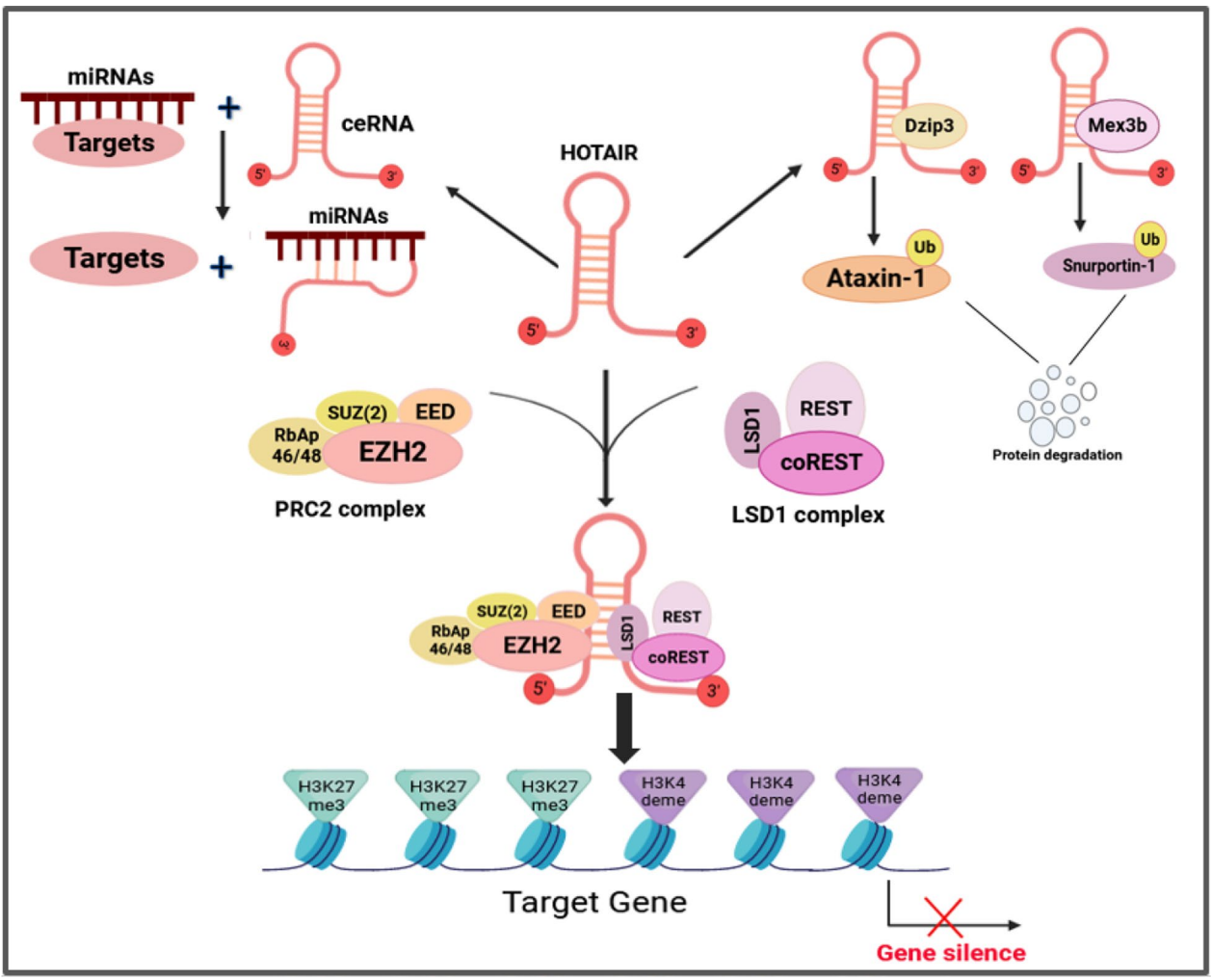

Fig. 1 Describes the role and molecular mechanisms of *HOTAIR* by listing all its major partners. First, *HOTAIR* binds to the PRC2 complex at its 5′-end and simultaneously forms compounds with the LSD1 complex at its 3′-end. The PRC2 complex and the LSD1 complex, which mediate H3K27 tri-methylation and H3K4me3 demethylation, respectively, facilitate gene silencing. Second, *HOTAIR* interacts with E3 ubiquitin ligases, including Mex3b and Dzip3, to promote the ubiquitination of Snurportin-1 and Ataxin-1, leading to their degradation. Third, HOTAIR acts as a competing endogenous RNA that interacts with miRNAs to enhance the expression of genes targeted by miRNAs

fragment on its 5' end. In addition, *HOTAIR* is essential for the occupation of PRC2 and the formation of H3K27me3 in a number of chromosomes [7].

HOTAIR alters gene transcription by binding to a DNA polypurine motif [12]. Nevertheless, several studies have proposed an alternative mechanism for the interaction of *HOTAIR* and PRC2. This model suggests that the PRC2 complex interacts with *HOTAIR* via short repeats of consecutive guanines in the *HOTAIR* sequence, rather than via a specific structural domain [13–15]. In addition, *HOTAIR* is important for the lysine-specific demethylase 1 (LSD1) complex [16, 17]. Gene expression can be repressed by the combination of LSD1, REST, and CoREST by decreasing H3K4me3 [18]. As a marker of transcriptional activation, H3K4me3 can help identify a gene, and demethylation of H3K4 correlates with transcriptional inactivation. HOTAIR is able to bind to the complex via a 646 bp region in the last exon of LSD1 [13]. Interestingly, *HOTAIR* interacts with LSD1 and PRC2 using distinct domains—the LSD1 complex interacts with the 3′ end of *HOTAIR* (1500–2146 nt), while the PRC2 complex interacts with the 5′ end of *HOTAIR* (1–300 nt) [13, 16, 17]. Additionally, by using the ubiquitin–proteasome system as a scaffold for chromatin changes, *HOTAIR* can serve as a method for modulating levels of proteins. Particularly, *HOTAIR* engages with the E3 ubiquitin ligases Mex3b and Dzip3 to promote ubiquitination and subsequent destruction of Snurportin and Ataxin-1 [19, 20]. In addition, *HOTAIR* promotes the expression of genes targeted by miRNA by acting as a competitive endogenous RNA sponge (ceRNA) for a number of miRNAs [6].

HOTAIR and signaling pathways

HOTAIR is involved in regulating cell differentiation and the development of various tissues throughout the body. Before it functions, it primarily enters the nucleus directly and undergoes post-translational modification. Figure 2 illustrates how *HOTAIR* interacts with multiple signaling pathways in different types of cancer.

Wnt signaling pathway

The dysregulation of Wnt/β-catenin signaling due to genetic and epigenetic alterations has been established to influence various cancer types [21]. The *HOTAIR* gene has been found to play a role in activating the Wnt signaling pathway, which promotes tumor progression. When *HOTAIR* is expressed abnormally, it causes the delocalization of the PRC2 protein and trimethylation of the H3K27 protein in the promoter region of WIF-1 [22]. This results in chromatin being silenced, suppressing the Wnt/β-catenin signaling pathway. The atypical stimulation of the Wnt pathway degrades the cytoplasmic β-catenin APC/Axin1 complex, increasing nuclear β-catenin levels and results in the expression level of genes such as *cyclinD1* and *MMP7*, facilitating tumor metastasis, invasion, and angiogenesis [23, 24].

HOTAIR is reported to function in HeLa cells, significantly contributing to their invasion and proliferation. The knockdown of *HOTAIR* in HeLa cells decreased the activity of the Wnt/β-catenin signaling pathway and increased the mRNA levels of its negative regulators by reducing the methylation of their promoters [25]. The main consequence of this is to downregulate the *SOX17*, *PCDH10*, *AJAP1*, and *MAGI2* genes, while their methylation patterns are upregulated. Moreover, Wnt/β-catenin is activated by *HOTAIR* overexpression, which increases the level of cyclin D1, c-Myc, and GSK-3β and improves leukemia cell survival and growth [26]. In addition, overexpression of *HOTAIR* stimulates the Wnt/β-catenin signaling pathway, which in turn stimulates ovarian cancer cell proliferation and invasion and drives cell cycle progression [27]. Numerous forms of tumor metastasis are associated with abnormal activation of the Wnt/β-catenin pathway, usually caused by genetic and epigenetic alterations [28]. Mutations in the *HOTAIR* gene can decrease the function of the Wnt/β-catenin pathway and increase the messenger RNA levels of its inhibitors [25].

PI3K/AKT/MAPK pathway

The PI3K/Akt signaling system influences the expression of upstream and downstream genes, which in turn influence cell proliferation, cell death, and metastasis [29, 30]. *HOTAIR* can induce methylation of the promoter of the *PTEN* gene, which leads to its silencing. *PTEN* is a tumor suppressor gene that is frequently mutated in human tumors and suppresses the PI3K signaling pathway to prevent cancer growth [31]. High levels of *HOTAIR* inhibit *PTEN* expression and activate Akt signaling, causing downstream genes of the Akt pathway to be expressed abnormally [32]. When Akt inhibits p53 activity, Bcl-2 expression increases and Bax expression decreases. According to Yu et al., knocking down *HOTAIR* in MCF7 cells significantly upregulates *p53* expression and significantly downregulates *MDM2*, *JNK*, *Akt*, *MMP2*, and *MMP9* expression [33]. Furthermore, Akt signaling activation increases the activity of the cyclin-dependent protein kinase complex, which in turn stimulates the proliferation of cancer cells by inhibiting the expression of *p21* [34].

According to research findings, *HOTAIR* promotes osteosarcoma cell proliferation through the activation of AKT/mTOR signaling by increasing the expression levels of p-PI3K, p-AKT, and p-mTOR [32]. The *HOTAIR*/*miR-326*/*FUT6* axis controls fucosylation of CD44, which in turn stimulates the PI3K/AKT/mTOR pathway,

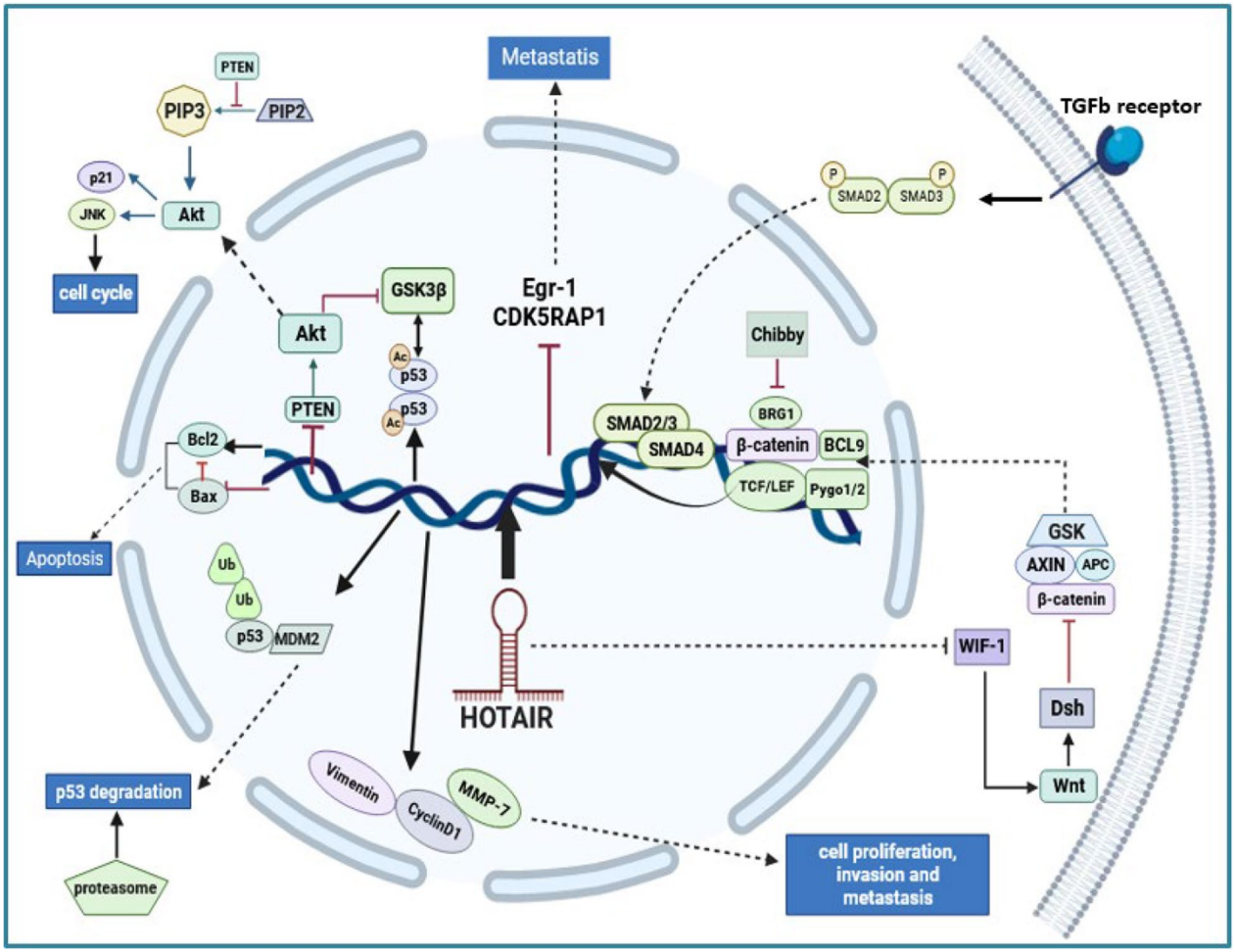

Fig. 2 *HOTAIR* and main signaling pathways in cancer. HOTAIR promotes cancer growth by regulating multiple signaling pathways, including the *TGFb* signaling, Wnt signaling, JNK pathway, p53 signaling, and Akt signaling. Activation or inhibition of these pathways leads to apoptosis, differentiation, invasion, metastasis, and abnormal cell division

promoting the development of colorectal cancer [35]. In chronic leukemia cells KCL22 and K562, both inhibition of *HOTAIR* and overexpression of miR-143 inhibit proliferation and stimulate apoptosis by altering PI3K/AKT pathway proteins [36]. *HOTAIR* suppresses the expression of *FGF1* by upregulating the expression of *miR-326*, and cell behavior is affected by this inhibition in multiple ways, including inhibition of migration, invasion and proliferation during G0/G1 phase. In addition, *miR-326* stimulates cell cycle arrest and cell death, all of which is achieved through the PI3K/AKT and MEK1/2 signaling pathways [37].

TGF-β pathway

Normal tissue repair and development is highly dependent on epithelial-mesenchymal transition (EMT), a process in which epithelial cells become mesenchymal cells. However, in the context of cancer cells, this transition can also be triggered, leading to invasion and spread of the tumor to distant sites, known as metastasis [38]. Transforming growth factor beta (TGF-β) is a protein that plays a crucial role in the control of cell growth, mobility and differentiation. It has been shown to be involved in the process of EMT. New research suggests a clear link between HOTAIR and the process of EMT, which is primarily regulated by the TGF-β signalling pathway [39]. TGF-β1 induces EMT and metastasis in breast cancer cells by activating HOTAIR expression through *SMAD2/3/4* binding to the *HOTAIR* promoter site [39]. TGF-β1 also mediates EMT through targeting CDK5 signaling through H3K27 tri-methylation. Moreover, HOTAIR exerts its influence on the EMT by promoting gene transcription and regulating gene expression through epigenetic mechanisms [4, 7]. As for miR-217, HOTAIR acts as ceRNA and sponges *miR-217* to alter *HIF-1a*

expression to promote EMT via *miR-217/HIF-1a/AXL* axis [40]. In addition, *HOTAIR* plays a role in suppressing *miR-7* expression, leading to an increase in *SETDB1* expression specifically in breast cancer stem cells. This upregulation of *SETDB1* contributes to the promotion of the EMT process [41].

VEGF pathway

Tumor angiogenesis is well-known to play an important role in tumor metastasis, with vascular endothelial growth factor (VEGF) being a highly specific angiogenesis factor. VEGF is a critical molecule that plays a vital role in both the vascular endothelial cells and extracellular matrix [42]. *HOTAIR* directly participates in the promotion of VEGFA transcription by activating the transcription of the 2.3 kb *VEGFA* promoter [43]. Matrix metalloproteinases (MMPs) are closely associated to the breakdown of extracellular matrix proteins, which raises the possibility that cancer cells will multiply and invade [44]. In addition, a specific member of the family of heat shock proteins 70, the so-called glucose regulatory protein 78, was identified in NPC cells as a target for the antiangiogenic effects of *HOTAIR* [45]. Previous research has suggested that knockdown of *HOTAIR* expression results in decreased cell proliferation. This decrease in proliferation is correlated to reduced expression of VEGF and MMP-9, two factors crucial for cell motility and migration in hepatocellular carcinoma [46]. In a study conducted by Liu et al., it was demonstrated that *HOTAIR* is upregulated in non-small cell lung cancer (NSCLC) tissues. This upregulation of *HOTAIR* contributes to the partial promotion of cell invasion and migration by downregulating HOXA5. Additionally, knockdown of *HOTAIR* results in decreased protein expression levels of MMP9 and MMP2 in NSCLC cells. These findings suggest that *HOTAIR* may play a role in modulating the expression levels of MMPs and HOXA5, thereby influencing the invasive and migratory capabilities of NSCLC cells [47].

Clinical application of HOTAIR

Several studies have investigated the effects of the different *HOTAIR* variants on susceptibility to different types of cancer. Furthermore, the detection of *HOTAIR* offers a non-invasive approach that can provide important prognostic, diagnostic and therapeutic insights in various malignancies. This is due to *HOTAIR*'s ability to target cancer-associated signaling pathways, which offers several advantages over invasive diagnostic techniques. By exploiting these properties, *HOTAIR* detection promises to become a valuable tool for cancer treatment.

Cancer susceptibility

Gene polymorphisms can have a major impact on normal biological activities, particularly those associated with cancer risk. In the human genome, single nucleotide polymorphisms (SNPs) are a major type of genetic variation. SNPs can occur in genes that regulate various cellular mechanisms, including but not limited to gene expression, protein function and signaling pathways. Studies such as the genome-wide association studies have shown that SNPs in non-coding regions can lead to changes in the expression and function of lncRNAs that ultimately influence an individual's susceptibility to cancer [48].

The first meta-analysis examining the relationship between *HOTAIR* lncRNA polymorphisms and susceptibility to lung cancer analyzed six studies with 1,715 patients and 2,745 controls and identified the rs1899663 C > A polymorphism in *HOTAIR* as a significant risk factor for lung cancer [49]. Variants in the *HOTAIR* gene, such as rs920778, have been associated with a higher risk of many cancers, including lung cancer, breast cancer, and ovarian cancer [50–52]. Breast cancer (BC) risk and cholangiocarcinoma are associated with another *HOTAIR* SNP, rs4759314 [51, 53]. Additionally, rs47593 and rs1899663 are associated with the development of ovarian cancer (OC) [54], while rs4759314 and rs200349340 are strongly associated with susceptibility to pancreatic cancer [55]. Other *HOTAIR* SNPs, such as rs7958904, escalate the likelihood of developing cervical cancer and colorectal cancer [56, 57]. However, it should be noted that not all SNPs in the *HOTAIR* gene increase the risk of cancer. In the case of women from southeastern Iran, two specific SNPs, rs12826786 and rs1899663, are actually found to have a negative correlation with breast cancer risk [58]. The influence of variant rs1899663 (G > T) can cause changes in *HOTAIR* expression through its impact on the binding affinity of multiple invasive, including *PAX-4*, *SPZ*-1, and *ZFP281* [59].

SNP-SNP interactions can amplify gastric cancer risk, as demonstrated in a high-risk Iranian population where specific genetic variants in the oncogenic lncRNAs *HOTAIR* and *HOTTIP*, particularly between *HOTAIR* rs1899663 and *HOTTIP* rs1859168, significantly heighten susceptibility [60]. Significantly predicting HCC risk, a three-factor model including Hepatitis B surface antigen (HBsAg) status and SNPs rs12427129 and rs3816153 was highlighted on hepatocellular carcinoma (HCC) risk in a southern Chinese population. The findings revealed significant associations of SNPs rs12427129 and rs3816153 with HCC risk, influenced by their interaction with HBsAg status, underscoring the importance of these genetic variations and their interactions in understanding HCC susceptibility [61].

The importance of ethnicity for the effects of *HOTAIR* SNPs is supported by the correlation between rs12826786 and increased gastric cancer risk in the Chinese population and increased BC risk in Egyptian women [62, 63], but not in the Turkish population [124]. Similarly, rs1282678 exhibits a negative correlation with the development of BC in women residing in southeastern Iran, likely due to differences in genetic background and ethnicity [64]. The *HOTAIR* SNPs rs12427129 and rs3816153 are not only associated with precancerous status such as HBV, but also predict the likelihood of developing hepatocellular carcinoma, which is a major cause of liver cancer [65]. Several meta-analyses examining the impact of *HOTAIR* SNPs on cancer risk have consistently shown that the rs920778 variant is strongly linked to an elevated risk of cancer across various ethnic groups [66, 67]. Table 1 provides an overview of the *HOTAIR* gene variations that have been studied for their effects on various cancer risks and their clinical significance in different ethnic groups.

Cancer diagnosis

LncRNAs serve as valuable tools for cancer detection in three different ways: as biomarkers detectable in the bloodstream and in stool samples, and as radioactive targets. These LncRNAs can be introduced into the human bloodstream in the form of microvesicles, exosomes or as components of protein complexes, resulting in the presence of highly stable circulating LncRNAs in body fluids such as blood and urine [96]. Therefore, *HOTAIR* is a promising non-invasive biomarker for the identification and prognosis of various malignancies [97, 98] (Table 2).

In the diagnosis of non-small cell lung cancer, *HOTAIR* plasma outperformed CEA level (AUC = 0.73) in terms

Table 1 *HOTAIR* gene variants and cancer risk

HOTAIR variant	Effect	Ethnicity	Cancer	References
rs920778 C > T	↑ risk	Chinese, Iranian and Turkish	BC	[58, 62, 68, 69]
		Chinese	LC	
		Chinese	CC, HCC, ESCC, OSCC and PTC	[70–74]
	Protective role	Chinese	OC	[75]
rs1899663 G > T	↑ risk	Portuguese	Glioma and PCa	[76, 77]
		Iranian	BC and PCa	[78, 79]
		Chinese	OSCC, LC and Neuroblastoma	[73, 80, 81]
	Protective role	Saudi	CRC	[82]
		Iranian	BC, NHL, and CRC	[58, 83, 84]
	No association	Chinese	BC	[62, 69]
rs4759314 A > G	↑ risk	Chinese	Cervical cancer, ESCC, PTC, GC, and HCC	[71, 72, 74, 85, 86]
		Greece, Chinese	PC	[55, 87]
	No association	Chinese	HNSCC	[88]
		Southeast Iranian	BC	[68]
	Protective role	Chinese	BC	[51]
		Iranian	PCa	[89]
		Chinese	Cervical cancer, OSCC, LC, BC, GC, HCC, ESCC, and Neuroblastoma	[71, 74, 79–81, 90]
rs12826786 C > T	↑ risk			[68]
		Turkish	BC	
		Iranian	PCa	[78]
	Protective role	Chinese	GCA and Neuroblastoma	[81, 91]
		Southeast Iranian	BC	[58]
		Saudi, Turkish	CRC	[82, 92]
	No association	Turkish	GC	[93]
rs7958904 G > C	↑ risk	Portuguese	Glioma and PCa	[76, 77]
		Chinese	BC and Cervical cancer	[91]
	Protective role	Chinese	CRC and OS	[82, 90]
	↑ risk	Chinese	Neuroblastoma and Bladder cancer	[81, 94]
rs2366152 A > G	↑ risk	Iranian	CRC	[84]
	↑ risk	Indian	Cervical cancer in HPV positive patients	[95]

Table 2 Diagnostic value of HOTAIR in human cancers

Study	Cancer type	Sample type	AUC	Key findings
Li et al. [97]	NSCLC	Plasma (*HOTAIR* and CEA)	0.84	Combination of HOTAIR and CEA improved diagnostic accuracy (AUC = 0.84)
Yao et al. [99]	NSCLC	Plasma	–	HOTAIR has high specificity (86.9%) for pathological staging of NSCLC
Lou et al. [100]	HCC	Serum (*HOTAIR*, *ICR*, *BRM* + AFP)	0.998	Combination of LncRNAs with AFP achieved maximum diagnostic accuracy
Liu et al. [101]	CC	Vaginal Discharge	0.9723	HOTAIR showed higher diagnostic performance in vaginal discharge than serum
Liu et al. [101]	CC	Serum	0.8518	Promising diagnostic marker; warrants further investigation
El-Fattah [102]	BC vs Fibroadenoma	Serum	–	Differentiation between BC and fibroadenoma is possible via serum HOTAIR levels
Gharib [103]	CRC	Fecal Colorectal Cancer Cells	0.9236	HOTAIR detection in fecal samples enables early detection of CRC

Non-Small Cell Lung Cancer (NSCLC), Hepatocellular Carcinoma (HCC), Cervical Cancer (CC), Alpha-fetoprotein (AFP), Breast Cancer (BC), Colorectal Carcinoma (CRC)

of diagnostic accuracy. Notably, the combination of CEA and *HOTAIR* expression significantly improved diagnostic accuracy (AUC = 0.84). Consequently, the combination of *HOTAIR* and CEA in plasma may prove to be an effective biomarker for the detection and follow-up of NSCLC [97]. Similarly, Yao et al. conducted a prospective study involving 148 patients in which *HOTAIR* was found to have significant diagnostic value for detecting the pathological staging of NSCLC with a high specificity of 86.9% and sensitivity of 52.3% [99]. A meta-analysis of 16 studies demonstrated that exosomal *HOTAIR* shows moderate diagnostic accuracy for NSCLC, with pooled sensitivity of 0.74, specificity of 0.78, and an AUC of 0.80 [104]. Remarkably, serum levels of the LncRNAs *HOTAIR*, ICR, and BRM were reported to be significantly higher in HCC patients compared to healthy individuals. When these three LncRNAs were combined with alpha-fetoprotein, the diagnostic accuracy for HCC reached its maximum potential, as indicated by an impressive AUC value of 0.998, a sensitivity of 98.4% and a specificity of 100.0% [100].

As reported by Liu et al., *HOTAIR* shows potential as a diagnostic tool for cervical cancer. The study found that *HOTAIR* had an AUC of 0.9723 for vaginal discharge, with a sensitivity of 92% and a specificity of 98%. For serum samples, *HOTAIR* achieved an AUC of 0.8518, with a sensitivity and specificity of 79% and 94%, respectively. These results indicate that *HOTAIR* is a promising diagnostic marker for cervical carcinoma that warrants further investigation and potential clinical applications [101]. These reports propose that *HOTAIR* is a promising marker for cervical carcinoma diagnosis and treatment, with a higher diagnostic performance observed in vaginal discharge than serum. Serum expression levels of *HOTAIR* may also serve as a diagnostic tool to differentiate between BC and fibroadenoma patients [102]. In addition, urine samples containing *HOTAIR*-containing exosomes can be used as biomarkers for patients with urothelial carcinoma (UC) [105]. Analysis of stool samples from patients with colorectal carcinoma (CRC) shows the presence of CRC cells. By detecting *HOTAIR* expression in fecal colorectal cancer cells, fecal examination provides a rapid and low-risk method for direct assessment of the condition of the colon and rectum and enables early detection of colorectal cancer [103].

Cancer prognosis

Previous studies provided clear evidence of a link between dysregulation of *HOTAIR* expression and tumor cell proliferation and metastasis in various cancers (Table 3). This section addresses the prognostic significance of *HOTAIR* dysregulation in various human malignancies.

Leukemia

Acute leukemia, which includes both acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML), is a life-threatening condition characterized by clonal disorders of hematopoietic stem cells [147]. Elevated levels of *HOTAIR* expression have been spotted in AML patients compared to healthy individuals. This increased expression of *HOTAIR* is positively correlated with the expression of *EZH2*, *LSD1*, *DNMT3B*, and *DNMT3A*. These molecular interactions control the *PRC2* and *LSD1* complex, which may contribute to the onset and spread of leukemia [148]. Recent studies have revealed that *HOTAIR* and c-kit genes operate as separate prognostic indicators for 12p chromosomal associated AML [149]. In addition, *HOTAIR* has been found to modulate resistance to imatinib by activating the PI3K/Akt-dependent pathway in patients with chronic myeloid leukemia [150].

Table 3 Prognostic value of *HOTAIR* in human cancers

Cancer type		Sample	Clinical manifestations	References
Blood cancer	Leukemia	Tissue	Chemoresistance	[106]
	Lymphoma	Blood	Poor overall survival	[107]
Bone cancer	Osteosarcoma	Tissue	Poor prognosis	[108]
	Chondrosarcoma	Tissue	Poor prognosis, tumor stage, and cancer progression	[109]
Skin cancer	CSCC	Tissue	Recurrence and survival	[110]
	CSCC	Tissue	increased stemness and cancer progression	[110]
	Melanoma	Tissue	lymph node metastasis	[111, 112]
Head and neck cancer	GBM	Tissue	Grade	[113, 114]
	GBM	Serum	Grade, poor disease-free survival and overall survival	[4, 114]
	NPC	Tissue	Tumor size, stage, lymph node metastasis, and poor prognosis	[115]
	LSCC	Tissue	Recurrence, grade, T stage, and risk of lymphatic metastasis	[115–117]
	TC	Tissue	Tumor size, depth of infiltration, lymph node metastasis, TNM stage, and distant metastasis	[118]
	TC	Tissue	Tumor density, morphology, enhanced residual circles, and calcification	[119]
Lung cancer	SCLC	Tissue	Lymphatic infiltration and recurrence	[120]
	NSCLC	Tissue	Lymph node metastasis and TNM stage	[121]
	Lung adenocarcinoma	Tissue	Poor prognosis	[122]
Digestive cancer	ESCC	Serum	Distant metastasis and TNM stage	[122, 123]
	ESCC	Tissue	Poor prognosis	[124]
	GC	Tissue	Tumor size, stage, and differentiation	[125]
	GC	Tissue	Chemoresistance and GC with H. Pylori infection	[126, 127]
	CCA	Tissue	Tumor size, TNM stage, and recurrence	[128]
	HCC	Tissue, blood	Recurrence, metastasis, Tumor size, poor prognosis and survival	[129, 130]
	HCC	Tissue	HBV-induced hepatocarcinogenesis and pre-cancerous lesions of HCC and	[131, 132]
	PC	Tissue	Overall survival and N stage	[133]
	CRC	Tissue	Venous infiltration, distant metastasis, and poor prognosis	[134]
	CRC	Tissue	Prognostic feature of liver metastasis and low overall survival	[53]
	CRC	Tissue	Microbiota-mediated colorectal carcinogenesis and progression	[135]
Breast cancer	Metastatic breast cancer	Tissue	Metastasis and survival	[4]
	DCIS	Tissues	Stage	[123]
Genitourinary cancer	UC	Tissue	Poor recurrence-free survival, disease-free survival, and disease-specific survival	[136]
	UC		HOTAIR rs920778 correlated negatively with lymph node metastasis	[137]
	PCa	Tissue	Therapeutic target and prognostic value	[138]
	RCC	Tissue	Fuhrman grade and stage, and lymph node and lung metastasis	[139, 140]
	CC	Tissue	Overall survival and lymph node metastasis	[141]
	OC	Tissue	Stage, tumor histological grade, lymph node metastasis, overall survival, and disease-free survival	[142, 143]
	OC	Tissue	Chemotherapy-resistant and recurrence	[144]
	EC	Tissue	lymphovascular interstitial infiltration, lymph node metastasis, myeloid infiltration, relapse-free survival, and disease-free survival	[145, 146]
	EC	Tissue	Grade and the depth of lymph node metastasis myeloid infiltration, and lymphovascular interstitial infiltration	[145]

Lymphoma

About 3% of cancer deaths worldwide are attributed to lymphoma [151]. Higher *HOTAIR* levels in diffuse large cell lymphoma (DLBCL) are correlated to increased IPI score and progression to the more severe Ann Arbor stage [152]. Remarkably, men diagnosed with AL and DLBCL have displayed elevated *HOTAIR* expression levels when compared to their female counterparts. This indicates that *HOTAIR* could be used as a prognostic marker for predicting poor outcomes in lymphoma

patients [153]. Recently, Senousy and colleagues found that elevated levels of *HOTAIR* were associated with non-responsiveness to R-CHOP treatment in DLBCL patients, and that *HOTAIR* was an independent predictor of R-CHOP failure [107].

Myeloma

In a recent study, multiple myeloma (MM) patients were found to have significantly higher expression of *HOTAIR* in serum, bone marrow and primary CD138 + cells than normal controls [154]. Similarly, *HOTAIR* levels were shown to be significantly elevated in newly diagnosed MM patients who had achieved CR or VGPR, and a correlation was found between *HOTAIR* levels and the percentage of malignant plasma cells in the bone marrow as well as disease stage [155]. In addition, *HOTAIR* has been shown to improve MM cell survival and chemoresistance to DEX via the JAK2/STAT3 pathway, proposing that *HOTAIR* may be a potential therapeutic target for MM [156].

Osteosarcoma

HOTAIR is highly expressed in osteosarcoma tissues and cells, and an increase in its expression is closely associated with advanced tumor stages and high histological grade [157]. A lower overall survival rate has also been linked to high *HOTAIR* levels. Recently, Li et al. displayed that downregulation of *HOTAIR* is predictive of an unfavorable prognosis in osteosarcoma patients, as it leads to an overexpression of *LRP5* which then activates Wnt signaling. In addition, *HOTAIR* silencing makes osteosarcoma cells more sensitive to the *DNMT1* inhibitor, and it regulates apoptotic and viability processes in osteosarcoma cells via the *HOTAIR-miR126-CDKN2A-DNMT1* axis [158].

Chondrosarcoma

In patients with chondrosarcoma, *HOTAIR* expression is associated with tumor stage and poor prognosis [109]. In CS cells, *HOTAIR* can induce DNA methylation of miR-454-3p by employing *DNMT1* and *EZH2*. Additionally, miR-454-3p operates on the autophagy-related gene 12 (ATG12) and signal transducer and activator of transcription 3 (*STAT3*) to activate apoptosis and decrease autophagy in cases of *HOTAIR* deficiency. Moreover, suppression of *HOTAIR* leads to G0/G1 cell cycle arrest and apoptosis in both in vivo and in vitro chondrosarcoma models, effectively inhibiting cell growth [159]. Recently, Feng et al. revealed that *HOTAIR* is significantly overexpressed in synovial sarcoma (SS), and this overexpression is associated with distant metastasis, AJCC staging, and histologic grade [160]. In SS cells, *HOTAIR* inhibition suppresses cellular proliferation, migration, and invasion. It promotes the G1/G0 phase of the cell cycle inhibits the G2/S phase [160].

Skin cancer

Skin cancer manifests in two primary forms: Melanoma and non-melanoma skin cancer (NMSC) [161]. Among non-melanoma skin cancers, cutaneous squamous cell carcinoma (CSCC) is the second most prevalent, which originates from epidermal keratinocytes [162]. *HOTAIR* expression levels are higher in CSCC tissue in compare with to normal tissue, and this increased level is positively associated with poorer OS in CSCC patients [110]. Recurrent CSCC tissue was found to exhibit higher *HOTAIR* expression levels than non-recurrent CSCC tissue, suggesting a link between *HOTAIR* expression and CSCC recurrence [110]. In addition, *HOTAIR* expression has been correlated with metastatic progression, showing an increase in both melanoma tissue and serum [111].

Glioblastoma

Of the brain tumors found in a clinical setting, glioblastoma (GBM) is the most frequent primary intracranial malignancy, contributing to roughly 55% of cases [163]. Abnormal overexpression of *HOTAIR* is observed in glioma tissue and is independently correlated with the grade of glioma [113, 114]. Increased expression of *HOTAIR* in serum is associated with worse outcome in patients with GBM and may be a novel biomarker for diagnosis and prognosis [164]. In addition, exosomes harboring *HOTAIR* in serum were revealed to be substantially linked to high-grade brain cancers [165]. Interestingly, a study showed that *HOTAIR* promotes proliferation and invasion of glioma cells by interacting with miR-301a-3p, a tumor suppressor, and indirectly increasing the expression of the oncogenic gene *FOSL1*. Inhibition of *FOSL1* or miR-301a-3p resulted in reduced tumorigenic behavior, highlighting the complex interplay between *HOTAIR*, *miR-301a-3p* and *FOSL1* in glioma progression [166]. *HOTAIR* was overexpressed independently of gene dosage, with DNA methylation of specific CGs correlating with its expression in GBM samples and cell lines, and was altered by 5-aza-2′-deoxycytidine in a cell line-dependent manner. *HOTAIR* was co-expressed with *HOXA9*, which binds directly to its promoter, and high *HOTAIR* levels were associated with lower overall survival in GBM patients independent of other prognostic factors [167].

Retinoblastoma

Retinoblastoma (RB) is a common intraocular malignancy that typically arises from the inactivation of the RB tumor suppressor gene [168]. Recent microarray analyzes have shown that *HOTAIR* is increasingly expressed in RB

tissues, contributing to RB metastasis [169]. *HOTAIR* showed increased expression in RB cells compared with normal retinal cells and exhibited high expression in *HXO-RB44* and Y79 cells. It functions as a ceRNA for *miR-20b-5p*, with a target on *RRM2* [170]. Recently, Dong et al. have conducted research that highlights the potential therapeutic target role of *HOTAIR* in RB. In their study, they demonstrated that inhibiting *HOTAIR* can effectively suppress the proliferative and invasive capability of RB cells [171].

Nasopharyngeal carcinoma

The distribution of nasopharyngeal carcinoma (NPC) is atypical, with a greater number of cases documented in East and Southeast Asia [172]. *HOTAIR* is highly expressed in NPC and is positively associated with lymph node metastasis, stage, and tumor size [115]. As the clinical stage of NPC increases, the expression of *HOTAIR* also increases and correlates with a worse outcome. Patients with NPC who have higher levels of *HOTAIR* generally have a lower overall survival rate [115].

Laryngeal cancer

Among head and neck tumors, laryngeal carcinoma (LC) is the second most common tumor; laryngeal squamous cell carcinoma (LSCC) accounts for 95% of cases [173]. There are numerous reports of abnormal *HOTAIR* expression in LSCC. For example, overexpression of *HOTAIR* in primary LSCC correlates significantly with T stage, pathologic grade, and risk of lymphatic metastasis when elevated [117]. Furthermore, previous reports have demonstrated differential expression of *HOTAIR* in recurrent and non-recurrent LSCC specimens, indicating its likely utility in detecting LSCC recurrence [116].

Thyroid carcinoma

Although treatment outcomes are favorable in most well-differentiated thyroid carcinomas (TC), there are still some patients who are unresponsive to conventional treatments, resulting in loss of hope for treatment [119, 174]. Knockdown of *HOTAIR* in the TC cell line resulted in a substantial suppression of proliferation, colony formation, and migration, accompanied by cell cycle retardation in the G1 phase [130]. Compared to normal and nodular goiter tissues, TC tissues show a significantly higher expression of *HOTAIR*. Significant associations were found between increased *HOTAIR* expression and tumor size, TNM stage, infiltration depth, lymph node metastasis, and distant metastasis [118]. Conversely, lower *HOTAIR* expression levels indicate a significantly better prognosis [119].

Lung cancer

Small cell lung cancer (SCLC) constitutes 15% of all lung cancer (LC) cases, while non-small cell lung cancer (NSCLC) makes up 80% of all cases [121]. High expression of *HOTAIR* is observed in SCLC, which is correlated to lymphatic infiltration and recurrence [120]. In addition, tumor tissue from NSCLC patients exhibits significant overexpression of *HOTAIR* expression, which strongly correlates with both lymph node metastasis and TNM stage [121]. Adenocarcinoma of the lung is the most frequent subtype of LC, and when patients with this cancer have increased *HOTAIR* expression, their prognosis tends to be worse. Simultaneous elevated expression of *HOTAIR* and the *EZH2* enhancer can acts as a prognostic marker for stage I lung adenocarcinomas and allows accurate prognosis prediction [122].

Breast cancer

Breast cancer (BC) poses the greatest risk for women worldwide and is associated with the highest mortality rate [175]. The first lncRNA found to be overexpressed in BC was *HOTAIR*, and its expression was associated with tumor development [52]. Gupta et al. observed that elevated *HOTAIR* expressions is seen in both primary and metastatic BC and promote an increase in histone H3 lysine 27 methylation via PRC2, thereby stimulating BC cell invasion and metastasis [4]. The abnormal expression of *HOTAIR* controls multiple signaling pathways and contributes to advanced tumor progression. In addition, ductal carcinoma in situ (DCIS) has a significantly increased expression of *HOTAIR*, which correlates with the progression of early breast cancer [123].

Esophageal cancer

The primary histopathological subtype is esophageal squamous cell carcinoma (ESCC), which is the eighth principal cause of cancer-related death worldwide [176]. Patients with ESCC have shown a correlation between their serum *HOTAIR* levels and their TNM stage, as well as distant metastasis [176]. ESCC tissue shows increased expression of *HOTAIR* and indicates a poorer prognosis in patients with high *HOTAIR* levels compared to those with low *HOTAIR* levels [22]. In addition, laboratory experiments have shown that *HOTAIR* stimulates the migration and invasion of ESCC cells.

Gastric cancer

Patients with gastric cancer (GC) who have elevated expression of *HOTAIR* have a poorer clinical prognosis [177]. Remarkably, subgroup analysis shows that patients with GC who have high *HOTAIR* expression have a highly significant association with worse prognosis. Tumor size,

stage, and differentiation of GC patients also correlate with *HOTAIR* levels [125]. Additionally, there is a correlation between elevated expression levels of *HOTAIR*, positive status for H. pylori infection, and the presence of precancerous lesions in GC [178]. Recently, *HOTAIR* was identified as a negative prognostic factor for GC and esophageal cancer based on bioinformatic analysis of TCGA databases [179]. Interestingly, Petkevicius et al. reported a study reflecting a negative H. pylori infection status in GC patients with high *HOTAIR* expression, which could be explained by population-based genetic differences and the intricate interplay between lncRNAs, miRNAs, and mRNAs [125, 126]. *HOTAIR* downregulated miR-217, which normally targets and reduces *GCP5* expression; thus, *HOTAIR* attenuation of *miR-217* increased *GCP5* expression, promoting GC development [180].

Liver cancer

The three forms of primary liver cancer are hepatocellular carcinoma (HCC), cholangiocarcinoma (CCA), and mixed subtypes. Of these, CCA is the least common subtype, while HCC is the most common, accounting for nearly 90% of primary cases [127]. Compared to normal bile duct tissue, *HOTAIR* exhibits high expression in both CCA and HCC tissues [181]. Increased levels of *HOTAIR* expression are associated with worse outcome in HCC and CCA. Tumor growth, metastasis, recurrence, and poor survival prognosis are correlated with high expression of *HOTAIR* in the tissues of HCC patients [128]. In the case of CCA, *HOTAIR*'s high expression levels significantly correlate with TNM stage, tumor size, and recurrence [109]. Additionally, in HCC, *HOTAIR* levels are correlated to precancerous lesions [128]. Furthermore, latest reports suggest a mechanism by which *HOTAIR* promotes HBV transcription and replication, thereby involving itself in HBV-induced HCC [132]. A study by Zhang et al. identified that *HOTAIR* SNPs rs12427129 and rs3816153 are associated with HCC risk in a Southern Chinese population, influenced by HBsAg status, with rs12427129 CT/TT genotype counteracting the harmful impact of rs3816153 GT/TT genotype, emphasizing the importance of SNP-SNP [61].

Pancreatic cancer

Pancreatic cancer (PC) stands as a prominent due to cancer-related mortality, primarily attributed to its strong association with metastasis and drug resistance [182]. In PC, tissues and cell lines exhibit overexpression of *HOTAIR*. According to a study by Kim et al., prostate cancer tissues have significantly higher *HOTAIR* levels than non-tumor tissues [133]. In addition, increased *HOTAIR* levels were associated with more aggressive tumors, suggesting that *HOTAIR* plays a pro-oncogenic role at PC. Moreover, increased *HOTAIR* expression promoted prostate cancer cell growth by increasing lactate formation, glucose uptake, and ATP. In addition, Kim et al. reported that increased *HOTAIR* expression intensified cell invasion and proliferation PC, suggesting a link between glucose metabolism, *HOTAIR*, and prostate cancer cell proliferation [183]. The levels of *HOTAIR* are also strictly correlated to the N stage and OS [133]. Similarly, a study by Ma and colleagues found that *HOTAIR* and hexokinase-2 (HK2) were upregulated in tumor tissue and serum levels can predict the presence of cancer and outcome. Overexpression of *HOTAIR* in cell lines increased lactate production, glucose uptake, ATP production and HK2 expression, suggesting that *HOTAIR* may enhance energy metabolism of cancer cells by regulating HK2 [183].

Colorectal cancer

Colorectal cancer (CRC) is one of the three most common and deadliest cancers in terms of both incidence and mortality. High expression of *HOTAIR* in CRC patients is closely associated with decreased OS, progressive tumor infiltration, venous infiltration, and distant metastases [134]. In addition, high *HOTAIR* expression has been found to be a possible prognostic marker for poor overall survival, and liver metastasis is a major cause of cancer-related mortality in CRC [53]. Furthermore, *HOTAIR* was linked to a potential mechanism of colorectal carcinogenesis and progression mediated by bacteria [135]. In another study, the long noncoding RNA *HOTAIR* was found to be upregulated in colorectal cancer tissues and its expression was negatively regulated by *miR-203a-3p* in colorectal cancer cell lines. Functional assays showed that both silencing of *HOTAIR* and overexpression of miR-203a-3p reduce cell proliferation and chemoresistance of colorectal cancer [184].

Bladder cancer

Urothelial carcinoma (UC), the most common subtype of bladder cancer, ranks seventh in terms of frequency of malignancy in wealthy countries. High *HOTAIR* expression in UC patients is strongly correlated with a unfavorable prognosis [135]. In contrast to other cancers, the activity of *HOTAIR* depends on its SNPs and can either promote or prevent cancer growth. Tung et al. found that female UC patients with *HOTAIR* rs4759314 had a worse prognosis and were more likely to develop a tumor; in contrast, UC patients who were younger or smokers and had *HOTAIR* rs12427129 had a higher T stage. Moreover, a negative correlation was observed between the presence of *HOTAIR* rs920778 and the development of lymph node metastases in patients with UC [185].

Prostate cancer

Prostate cancer (PCa) is the most common cancer in men and the exact causes remain unclear [186]. It has been found that in PCa patients, there is an inverse relationship between the expression of hepatocellular adhesion molecule (hepaCAM) in both blood and tissue and *HOTAIR* levels [138]. In the context of castration-resistant prostate cancer (CRPC), miR-193a serves as a tumor suppressor by hindering the growth and invasion of cancer cells. This suppression is achieved through a regulatory feedback loop involving *HOTAIR*, *EZH2*, and *miR-193a*. Therefore, disrupting this active loop could be a promising treatment approach for PCa [187]. Even under castrated conditions, the induction of *HOTAIR* has been demonstrated to promote the growth and invasion of PCa cells [146].

Renal cell carcinoma

Renal cell carcinoma (RCC) is a frequent cancer that causes over 90,000 deaths worldwide each year. RCC clinical tissues and cell lines have significantly higher *HOTAIR* expression than normal cell lines and tissues. According to association studies, *HOTAIR* is associated with various clinicopathological features and tumor progression in patients with RCC. Moreover, an increase in *HOTAIR* expression stimulates the growth and invasion of RCC cell lines. *HOTAIR* is also a crucial factor in the metastasis of renal cancer, as Katayama et al. have shown. According to them, *HOTAIR* regulates insulin-like growth factor-binding protein 2 to enhance the migration of renal cancer cells and is closely related to lung metastasis, lymph node metastasis and nuclear grade in renal cancer. Numerous studies have provided evidence that *HOTAIR* can promote the development of RCC through various mechanisms [188]. Furthermore, a recent study has revealed that *HOTAIR* and the androgen receptor interact to stimulate tumor angiogenesis and the presence of cancer stem cells both in vivo and in vitro in RCC cells [140].

Cervical cancer

One gynecologic cancer that is frequently detected and has a high mortality rate is cervical cancer (CC) [189]. HOTAIR expression levels in CC tissues are significantly higher than in adjacent non-cancerous tissues [190]. A recent study investigated the role of HOTAIR in the progression of CC. The study found that higher levels of *HOTAIR* correlated with more aggressive tumor behavior, including tumor staging, deep cervical invasion, and lymph node metastasis. Elevated *HOTAIR* levels were also associated with poorer DFS and OS in these patients [191]. While the results emphasize the importance of *HOTAIR* in the development and progression of cervical cancer, further studies with more patients from different regions are needed.

Ovarian cancer

Ovarian cancer is a form of cancer that starts in the ovaries. It can be difficult to detect as symptoms often appear later in the course of the disease. Elevated *HOTAIR* expression levels have been found to be strongly correlated with lymph node metastases, stage, overall survival and disease-free survival in OC tissue. *HOTAIR* levels are an independent prognostic factor in patients with OC [192]. In addition, OC has a high initial response rate to conventional platinum/paclitaxel therapy and is considered a chemosensitive tumor. Nevertheless, recurrence occurs in the majority of patients and the tumor rapidly develops drug-resistant properties. An important factor in the recurrence of OC is *HOTAIR* [144].

Endometrial cancer

The second most common type of gynecologic cancer is endometrial carcinoma (EC), which is associated with certain biological processes of tumor cells that are disrupted by lncRNAs [193]. According to one study, EC tissue had much higher expression of *HOTAIR* than normal tissue, and higher *HOTAIR* levels correlated positively with metastasis and lower overall survival [145]. Furthermore, patients exhibiting higher levels of *HOTAIR* expression experience significantly poorer OS than those with lower *HOTAIR* expression levels [145]. Furthermore, in vivo silencing of *HOTAIR* considerably inhibited endometrial tumorigenesis and reduced tumor size, highlighting its crucial role in EC development. Proliferation and invasion of EC cells were significantly hindered by suppression of *HOTAIR* expression. This was accompanied by a significant arrest of G0/G1 phase [194].

Therapeutic application

The therapeutic use of lncRNAs in the treatment of cancer has gained increasing attention in recent years. Their unique characteristics, such as tissue-specific expression and regulatory functions, make them attractive targets for therapeutic interventions. In particular, lncRNAs have shown significant potential in the areas of targeted therapy, immunotherapy, chemotherapy, and radiotherapy for cancer. In this section, we will explore the therapeutic potential of *HOTAIR* in these specific treatment modalities and discuss their implications for improving cancer treatment outcomes. Figure 3 illustrates different strategies for *HOTAIR* targeted therapy, radiotherapy, chemotherapy, and immunotherapy.

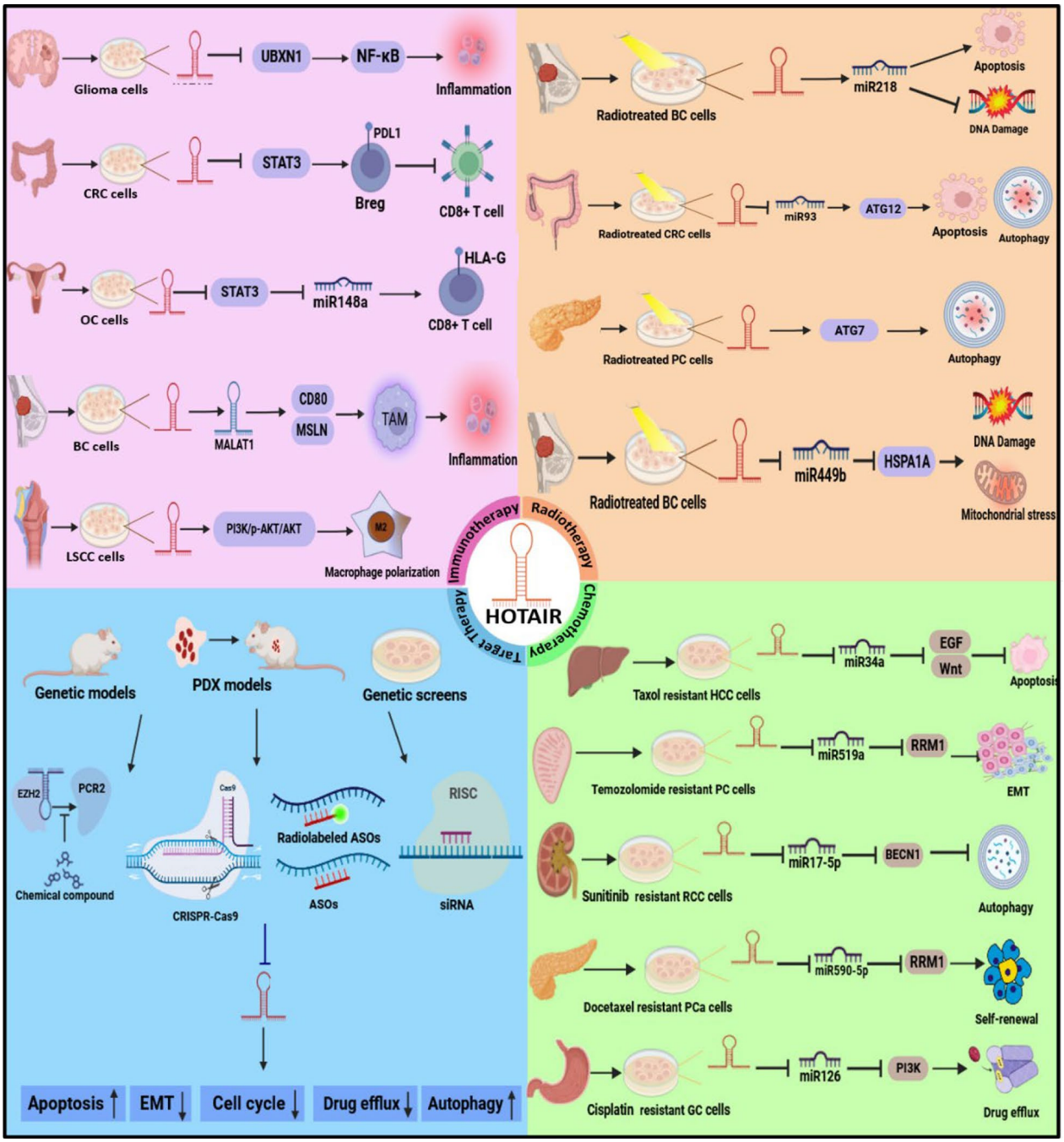

Fig. 3 Researchers are investigating several treatments for cancer that target *HOTAIR*, a long noncoding RNA (lncRNA) that is overexpressed in many types of cancer. Promising approaches include radiolabeled antisense oligonucleotides (ASOs), CRISPR/Cas9, small interfering RNA (siRNA), and chemical compounds such as ADQ and AQB. These treatments work by disrupting the function of *HOTAIR*, which plays a role in a number of cancer-related processes, including cell proliferation, invasion, metastasis, and immune suppression. *HOTAIR* inhibits the immune system by increasing inflammation, polarizing macrophages, promoting HLA-G expression, and lowering CD8 T cell activity. It also contributes to drug and radiation resistance by increasing DNA damage, EMT, cell cycle, and drug efflux while decreasing autophagy and apoptosis

Targeted therapy

A promising strategy for the treatment of cancer is likely to focus on lncRNAs. As lncRNA-based cancer therapeutics have shown promise in both cell and animal models, interest in their development has increased [195]. LncRNAs are recognized as promising candidates

for therapeutic intervention due to their variety of functions [196]. However, techniques for knocking down lncRNAs must consider their subcellular location. Targeting with small interfering RNA (siRNA) is the best strategy for cytoplasmic lncRNAs [53, 137], while antisense oligonucleotide (ASO) targeting is the best strategy for nuclear lncRNAs [197]. In addition, nucleases, aptamers and microRNAs are other techniques that can be used to suppress lncRNA activity. Reducing cytoplasmic and nuclear expression of *HOTAIR* molecules is the most popular experimental strategy to suppress *HOTAIR* [198]. In a recent study, Ren et al. developed a liposome-coated radiolabeled ASO targeting the LncRNA *HOTAIR*. The probe proved to be highly stable and targeted in mouse glioma tumor models, as clearly demonstrated by SPECT imaging [199].

To suppress *HOTAIR* expression in a dose-dependent manner, Ban et al. used synthetic short-interfering sense oligonucleotide DNA complementing *HOTAIR* transcripts. The tumor cells then became apoptotic, which allowed the researchers to study the effects of knocking down *HOTAIR* [200]. RNA-based therapeutics targeting *HOTAIR* have been the focus of subsequent studies. For instance, *HOTAIR*-sbid, an inactivated version of *HOTAIR*, was recently created as a novel strategy to block EMT in parenchymal malignancies [201]. The reduction in cell motility, anchorage-independent growth, invasiveness, and susceptibility to TGF-induced EMT in HCC is caused by the loss of the EZH2-binding domain in *HOTAIR*-sbid. Rather, it competes with endogenous wild-type *HOTAIR* for snail binding [201].

CRISPR/Cas9, a gene-editing tool, is a promising approach for cancer treatment. In one study, the long non-coding RNA *HOTAIR* was found to regulate prostate cancer invasion and metastasis by targeting hepaCAM. Using CRISPR/Cas9, the researchers silenced *HOTAIR* in DU145 and PC3 cells, resulting in a significant downregulation of *HOTAIR* expression. This downregulation affected the expression of invasion-related genes, with no effect observed when hepaCAM was also silenced [138]. *HOTAIR* is therefore associated with promoting the invasiveness and metastasis of prostate cancer by decreasing hepaCAM expression and activating the MEK/ERK signaling pathway. Furthermore, Picerno and colleagues employed CRISPR/Cas9 genome editing to generate *HOTAIR* knockout ARPC lines and revealed the central role of this lncRNA in maintaining the self-renewal capacity of ARPC by promoting proliferation and suppressing apoptosis [202]. Notably, the absence of *HOTAIR* led to ARPC senescence and a significant decrease in the expression of the stem cell marker CD133, which inversely correlates with ARPC senescence and regulates renal tubule regeneration after injury [202]. In ovarian cancer stem cells (OCSCs), Wang et al. effectively eliminated functional regions of *HOTAIR* using a paired CRISPR-guide RNA design without affecting neighboring protein-coding genes. The OCSC population was greatly reduced, stem cell properties were diminished, and OC cells were more sensitive to platinum treatment when *HOTAIR* was knocked out. These include the ability to form spheroids in vitro under minimal attachment conditions and inhibition of genes associated with stem cells, including ALDH1A1, Sox9, Notch3and PROM1 [203]. A thorough examination of RNA-seq and ATAC-seq data revealed that *HOTAIR* alters downstream gene expression in the NF-kB signaling pathway and affects global chromatin dynamics. A combination of an EZH2 inhibitor and a *HOTAIR* inhibitor in conjunction with chemotherapy significantly reduced tumor development and increased survival of mice in xenograft experiments with high-grade serous ovarian cancer cells [203].

Scientists have discovered inhibitors that can reduce the effect of *HOTAIR* without affecting its expression. For example, Ren et al. discovered that the 5' domain of *HOTAIR* is responsible for tumorigenesis and metastasis in glioblastoma and BC via an interaction with EZH2. They found that ADQ is a chemical molecule that specifically disrupts the link between *HOTAIR* and EZH2. In BC models, ADQ was observed to suppress tumor metastasis via the Wnt/β-catenin signaling pathway [204]. Similarly, Li et al. discovered AC1Q3QWB (AQB), which acts as an inhibitor of *HOTAIR* and EZH2 and prevents the recruitment of PRC2 [196]. Shi et al. later found that palbociclib in combination with AQB significantly reduced proliferation and metastasis of glioma cells with increased *HOTAIR* expression (205). Ozes et al. discovered that in ovarian and breast cancer cells, overexpression of *HOTAIR* prevented its binding to EZH2, which reduces tumor invasion and improved sensitivity to chemotherapy [206]. This shows that by screening larger libraries of natural and synthetic chemicals, it is possible to find new treatments that target *HOTAIR/EZH2*-dependent malignant tumors by interfering with their interaction with PRC2 complexes.

Chemotherapy

Chemotherapy is an important treatment method for controlling tumor growth and improving patient survival rates [207]. Several studies have shown that this method can reduce the mortality rate in people with advanced cancer or those who are not candidates for surgery. However, a major obstacle to cancer treatment is the development of acquired resistance to chemotherapy. Such resistance can lead to a higher mortality rate for patients and an increased risk of tumor recurrence. The development of resistance in cancer cells can be attributed to

many mechanisms, including EMT, suppression of cell apoptosis, autophagy, increased self-renewal of stem cells and alterations in drug metabolism and transport pathways. Table 4 provides an overview of current research studies involving chemotherapy and *HOTAIR*.

Apoptosis

In addition to the overexpression of pro-apoptotic proteins, cell survival factors also contribute to the regulation of drug-induced apoptosis. Recent research suggests that *HOTAIR* may influence chemotherapy resistance by modulating apoptotic pathways in cancer cells. For instance, one study demonstrated that in acute myeloid leukemia (AML), the suppression of *HOTAIR* increased sensitivity to doxorubicin and promoted apoptosis [232]. In addition, the *PI3K/AKT* signalling pathway was found to contribute to chemotherapy resistance and *HOTAIR*-mediated cell death in BC and GC [208, 209]. Similar results were found in various cancers of the digestive tract. For example, downregulation of methylenetetrahydrofolate reductase expression caused esophageal cancer cells to be sensitive to treatment with 5-fluorouracil (5-FU) by making them responsive to *HOTAIR* [210]. The downregulation of *HOTAIR* in hepatocellular carcinoma (HCC) reduced resistance to Taxol by counteracting miR-34a by the Wnt/β-catenin and Akt phosphorylation signaling pathways [211]. High *HOTAIR* levels in pancreatic cancer regulate the expression of death receptor 5 of TNF-related apoptosis ligands (*TRAIL)* and thus enhance cell resistance to apoptosis triggered by *TRAIL* [233]. Moreover, high *HOTAIR* expression in NSCLC correlates with lower overall patient survival. Knockdown of *HOTAIR* using small interfering RNA (si-*HOTAIR*) restored the sensitivity of NSCLC cells to cisplatin [212]. By adjusting cell apoptosis, *HOTAIR* affected cisplatin resistance in osteosarcoma. Experimental evidence indicates that suppressing *HOTAIR* enhanced cell mortality and decreases cisplatin resistance by the *miR-106a-5p*/*STAT3* signaling pathway [212].

Table 4 An overview of recent research studies focused on chemotherapy and *HOTAIR*

Mechanism	Cancer Type	Related drugs	Related genes or pathway	Reference
Apoptosis	BC	doxorubicin	PI3K/Akt/mTOR	[208]
	GC	cisplatin	PI3K/Akt and Wnt/β-catenin	[209]
	Esophageal	5-fluorouracil	MTHFR	[210]
	HCC	Taxol	Akt and Wnt/β-catenin	[211]
	NSCLC	cisplatin	Wnt	[212]
	Osteosarcoma	cisplatin	STAT3	[213]
EMT	NSCLC	gefitinib	Rb-E2F	[214]
	HCC	sorafenib	Vimentin and E-cadherin	[215]
	GC	cisplatin, adriamycin and mitomycin	PTEN	[216]
	BC	trastuzumab	MEK/MAPK and PI3K/AKT/mTOR	[217]
	PC	paclitaxel	Bcl-2 and Bax	[218]
	Glioblastoma	temozolomide	RRM1	[219]
Autophagy	NSCLC	crizotinib	ULK1	[220]
	Oral cavity carcinoma	cisplatin	Autophagy-related genes	[221]
	Endometrial	cisplatin	MDR, Beclin-1, and P-gp	[222]
	OC	cisplatin	ATG7	[223]
	RCC	sunitinib	Beclin1	[224]
Self-renewal ability	Lung	cisplatin	Klf4	[225]
	PC	gemcitabine	-	[226]
	PCa	docetaxel	STAT3	[227]
	OC	cisplatin	TBX3	[228]
Drug metabolism	GC	cisplatin	PI3K/AKT/MRP1	[229]
	CML	platinum	PI3K/AKT/MRP1	[150]
	HCC	cisplatin	MDR1	[230]
	HCC	imatinib	P-gp and BCRP	[231]
	Lung	cisplatin	MRP1, MDR1 and Wnt	[212]

EMT

Numerous studies have revealed that *HOTAIR* is involved in the control of epithelial-mesenchymal transition (EMT) in cancer cells, a process that leads to resistance to chemotherapy. Stimulation of EMT correlates *HOTAIR* expression in NSCLC with resistance to tyrosine kinase and epidermal growth factor inhibitors. As a predictor of gefitinib resistance, increased *HOTAIR* expression has been associated with decreased sensitivity to gefitinib [202]. Similarly, in HCC, overexpression of *HOTAIR* has been shown to accelerate resistance to sorafenib [215]. Based on mechanistic studies, si-*HOTAIR* has been shown to increase sorafenib sensitivity by upregulating miR-217, increasing E-cadherin levels, and decreasing vimentin levels. This suggests that EMT plays a role in *HOTAIR*-mediated chemotherapy resistance. *HOTAIR* overexpression was found to stimulate EMT in GC via control of the miR-17-5p/PTEN pathway. Thus, sensitivity to chemotherapeutic agents was enhanced by targeting *HOTAIR* [216]. The decline in *HOTAIR* level in BC led to the activation of the *PI3K/AKT/mTOR* and *MEK/MAPK* signaling pathways, influencing the expression of genes linked to the EMT and diminishing resistance to trastuzumab [217]. In PC, propofol treatment enhanced sensitivity to *PTX* by adjusting *HOTAIR*-mediated EMT [218]. Moreover, in glioblastoma, exosomal *HOTAIR* promoted temozolomide resistance via the *miR-519a-3p/RRM1* pathway, whereas silencing *HOTAIR* inhibited tumor growth, migration, invasion, and EMT [219]. Additionally, the expression of *HOTAIR*, which is favorably influenced by TRPM7, was significantly increased in glioma tissues in this study and was associated with a poor prognosis. While miR-301a-3p alone acted as a tumor suppressor, *HOTAIR* stimulated *miR-301a-3p* to upregulate FOSL1, a tumorigenic gene, thereby promoting proliferation and invasion of glioma cells [166].

Autophagy

During autophagy, lysosomes and autophagosomes, which contain cytoplasmic proteins or organelles, fuse to form autolysosomes. This fusion promotes cellular metabolism and the regeneration of certain organelles by enabling the degradation of the substances they contain [234]. Autophagy plays a complicated role in cancer that depends on a number of variables, including the cellular environment and the stage, grade, type and genetic associations of the tumor. By inhibiting the *ULK1* signaling pathway, which in turn slows autophagy, interrupting *HOTAIR* reduces treatment resistance to crizotinib in non-small cell lung cancer [220]. In another study, *HOTAIR* elimination in oral squamous cell carcinoma was found to increase sensitivity to cisplatin and decrease autophagy-related genes [221]. By inhibiting the *ULK1* pathway, which in turn slows autophagy, *HOTAIR* disruption reduces treatment resistance to crizotinib in non-small cell lung cancer [235]. Similar findings showed that *HOTAIR* modulates autophagy by the expression of P-glycoprotein (P-gp) and Beclin-1, which in turn affects cisplatin resistance in endometrial cancer. [222]. Furthermore, decreased *HOTAIR* expression increased cisplatin sensitivity by suppressing cisplatin-induced cell autophagy [223]. Ultimately, in renal carcinoma, *HOTAIR* promoted *BECN1*-mediated autophagy by targeting *miR-17-5p*, leading to enhanced resistance to sunitinib [224].

Self-renewal ability

Cancer stem cells (CSCs) are a type of cell that has the ability to self-renew and contribute to the development of tumors. The development and proliferation of tumor cells is caused by the abnormal process of self-renewal of CSCs. Liu et al. discovered that increased expression of *HOTAIR* leads to resistance to cisplatin in NSCLC cells. A potential target for treatment is the overexpression of *HOTAIR*, which increases CSC-related indicators and is associated with the expression of Klf4 [225]. In another study, gemcitabine was found to induce *HOTAIR* expression and act as a tumor promoter. This increase in *HOTAIR* reduced the chemosensitivity of PACN-1 CSCs and enhanced their self-renewal, growth, and migration abilities. This indicates that *HOTAIR* may be a possible target for PC therapy [226]. In BC, *HOTAIR* has been shown to be an essential modulator of the miR-34a/Sox2/p53 pathway, which in turn controls the ability of CSCs to self-renew [236]. By triggering the *STAT3* signalling pathway, HOTAIR increased the number of CSCs in prostate cancer patients. *HOTAIR* was found to act as a sponge for miR-590-5p, hindering its ability to bind to the upstream STAT3 molecule. Docetaxel resistance in PCa was successfully eliminated by targeting *HOTAIR* [227]. In OC, *HOTAIR* prevented suppression of *TBX3* levels by miR-206, which increased cisplatin resistance. This study suggests that *HOTAIR* could be a useful biomarker for the treatment of OC [228]. Additionally, increased levels of *HOTAIR* were detected in OC CSCs, promoting their ability to form colonies and spheroids. Interfering with the interaction between *HOTAIR* and *EZH2*, as well as DNA methylation, could improve chemosensitivity and prevent cancer recurrence [144].

Drug metabolism

Researchers have found that a significant contributor to multidrug resistance (MDR) in cancer cells is the decrease in drug accumulation. Juliano et al. discovered several decades ago that P-gp plays a role in actively pumping chemotherapeutics out of cancer cells, leading to drug cross-resistance. Through its modulation of ABC

transporters, which affects the efflux pump of the drug, *HOTAIR* leads to chemotherapy resistance. Increased *HOTAIR* levels have been shown to be associated with cisplatin resistance in GC. By directly binding to miR-126 and suppressing its expression, HOTAIR triggers the *PI3K/AKT/MRP1* pathway [229]. Similarly, downregulation of *HOTAIR* has been shown to increase susceptibility to imatinib via the *PI3K/AKT/MRP1* signalling pathway in CML cells [150]. In addition, knocking out *HOTAIR* in HCC decreases the expression of multidrug-resistant protein 1 (*MDR1*, sometimes referred to as *ABCB1*) and inhibits the function of *STAT3*, resulting in reduced resistance to cisplatin. This suggests that *HOTAIR* may be a viable therapeutic target for the reversal of MDR of HCC [230]. Subsequent studies have shown that *TGF-β*1 upregulates breast cancer resistance protein (BCRP) and P-gp in HCC via the *SMAD4/HOTAIR/miR-145* pathway, contributing to a unique MDR mechanism [231]. A thorough investigation in NSCLC found that the use of siRNA to reduce *HOTAIR* increases cell susceptibility to cisplatin by blocking the production of *MRP1*, *MDR1*, and the Wnt signaling pathway [212]. In CRC, it has been reported that *HOTAIR* knockdown and miR-203a-3p overexpression inhibited cell proliferation, reduced chemoresistance, and targeted β-catenin and GRG5 to inhibit Wnt/β-catenin signaling, with increased *miR-203a-3p* expression being crucial for these effects [184].

Immunotherapy

Immunotherapy, a form of cancer treatment, aims to fight cancer cells by activating the patient's immune system. It has been a major breakthrough in the field of tumor therapy over the past decade [237]. Multiple studies have suggested a link between HOTAIR and immune signaling within both innate and adaptive systems. *HOTAIR* was found to activate various proteins and signaling pathways involved in inflammation, such as *NF-κB*, *TNFα*, and *MAPK* in glioma [238]. It also promoted the accumulation of complexes and proteins associated with these inflammatory processes. In addition, *HOTAIR* affected T cell co-stimulation and immunologic response. By suppressing the expression of *UBXN1*, *HOTAIR* facilitated the phosphorylation and nuclear translocation of NF-κB and specifically promoted the phosphorylation of *IκBα*, which leads to elevated inflammation [238]. HOTAIR promotes tumor progression in glioblastoma by activating NF-κB, TNFα, MAPK, and other inflammatory signaling pathways through epigenetic modulation. This leads to increased PD-L1 expression, immune evasion, and aberrant activation of immune response processes, including T-cell co-stimulation, by facilitating IκBα phosphorylation, suppressing UBXN1, and promoting NF-κB phosphorylation and nuclear translocation [238]. Similarly, study by Xie and colleagues investigated how *HOTAIR* contributed to the phenotype of Bregs in CRC-derived exosomes, specifically in relation to *PDL1* expression (239). They found that tumor-derived *HOTAIR* turns B cells into regulatory cells characterized by *PDL1* expression and inhibits CD8 + T cell activity. Exosomal *HOTAIR* increased *PDL1* expression by suppressing pyruvate kinase M2 (*PKM2*) and activating *STAT3*. Tumor-infiltrating *PDL1*-positive B cells were positively correlated with exosomal *HOTAIR* in CRC patients.

HOTAIR has been found to interact with cytoplasmic miR-152 to modulate human leukocyte antigen (HLA-G) levels, which in turn promotes tumor escape mechanisms [240]. Similarly, upregulation of *HOTAIR* was found to modulate the expression of HLA-G through competitive binding of miR-148a in CC cells, suggesting that the *HOTAIR-miR-148a-HLA-G* axis may represent an interesting avenue for therapeutic applications [241]. Wang et al. provided evidence by co-culturing macrophages with LSCC exosomes highly expressing *HOTAIR* or transferred with *HOTAIR* mimetics that exosomal *HOTAIR* can activate the PI3K/p-AKT/AKT signaling pathway to induce polarization of M2 macrophages, and further showed that exo-treated M2 macrophages enhance proliferation, migration and EMT of LSCC [24]. According to Obaid et al., NF-kB activation controls the expression of Glut1, the transporter responsible for glucose uptake in macrophages. Inflammation induced by lipopolysaccharide (LPS) leads to increased Glut1 expression, and this regulation is remarkable. Knockdown of *HOTAIR* significantly inhibited LPS-induced *Glut1* expression in macrophages [242]. Furthermore, a recent report suggests that overexpression of *HOTAIR* is involved in the development of platinum resistance in OC through the induction of NF-κB activation during the DNA damage response via the reduction of Iκ-Bα, leading to a sustained increase in the expression of *NF-κB* target genes including interleukin-6 [243].

Bypassing the immune system is an important factor in the development, progression and recurrence of cancer. In leukemia, overexpression of *HOTAIR* has been associated with tumor immune evasion by enhancing stimulation of the Wnt/β-catenin pathway. This excessive activation of the pathway has been shown to strongly inhibit both innate and adaptive immunity in leukemia patients. Specifically, it has been associated with a decrease in NK cell activity, a lower ratio of CD4 + / CD8 + T subsets, decreased cytokine release in peripheral blood, and a decrease in immunoglobulin production by B lymphocytes [26]. In BC, Amer et al. found that *HOTAIR* has an upstream regulatory effect on *MALAT1* and that the downregulation of both leads to an increase in *CD80* and *MSLN* expression in in TAMs of

HER2 + and TNBC [244]. The ability to harness *HOTAIR* as a therapeutic target opens up new possibilities for improving patient outcomes and advance cancer immunotherapy, highlighting the significance of these findings.

Radiotherapy

Although radiotherapy is the most popular form of treatment for incurable and locally advanced malignancies, patients receiving radiotherapy often develop radioresistance [245]. Combining targeted *HOTAIR* approaches with conventional medications such as radiotherapy could improve therapeutic outcomes in addition to direct *HOTAIR* targets. By altering multiple molecular and cellular mechanisms, *HOTAIR* was discovered to increase radiosensitivity and also linked to radiation response in various cancer cell lines.

In BC, *HOTAIR* expression is elevated in both cells and tissues, and levels continue to increase after radiation. When *HOTAIR* is suppressed, BC cells are more sensitive to radiotherapy because miR-218, a ceRNA of *HOTAIR*, is upregulated, resulting in decreased cell survival, increased cell apoptosis, greater DNA damage, and cell cycle arrest [246]. Similarly, the levels of *HOTAIR* were positively associated with tumorigenicity of BC cells, while negatively correlated with radiosensitivity of BC cells. In clinical BC tissues, miR-449b-5p suppressed *HSPA1A* by binding to its 3′-UTR. However, *HOTAIR* as a competing sponge sequestered miR-449b-5p, abrogating its suppression of *HSPA1A*. Functionally, *HOTAIR* rendered BC cells less radiosensitive, but overexpression of miR-449b-5p or silencing of *HSPA1A* prevented *HOTAIR* from promoting BC cell development upon radiation exposure both in vitro and in vivo [247]. In addition, a study by Qian et al. found that overexpression of *HOTAIR* can serve as a reliable radiation marker in invasive ductal carcinoma (IDC) of BC tissues. In addition, *HOTAIR* has been found to recruit *EZH2* to the promoter region of the *MYC* gene, which in turn contributes to cell proliferation. Small molecule inhibitors of *EZH2* were able to prevent the overexpression of *HOTAIR*, thereby increasing the expression of DNA damage repair proteins *KU80*, *KU70* and ATM [248].

Based on the analysis of TCGA data, it was found that the overexpression of *HOTAIR* in PC is closely associated with tumor development. Further studies showed that knockdown of *HOTAIR* led to increased radiosensitivity and affected autophagy by upregulating the expression of *ATG7* in PC cells [249]. To confirm these results, rescue experiments with rapamycin were performed. Activation of autophagy by rapamycin administration reversed the inhibitory effects on cell proliferation and colony formation caused by knockdown of *HOTAIR*, while promoting apoptosis. This suggests that regulation of autophagy plays a critical role in *HOTAIR* knockdown-mediated promotion of radiosensitivity in PC cells [249]. In laryngeal cancer (LC) cells, exosomes derived from LC were found to have a detrimental effect on radiosensitivity. *HOTAIR* was found to act as a ceRNA for miR-454-3p, thereby regulating the activity of *E2F2* in LC cells, and knockdown of *HOTAIR* resulted in a decrease in radiosensitivity of LC cells [250]. In colorectal carcinoma, the expression of *HOTAIR* is significantly increased in plasma samples from patients who have undergone radiotherapy and in colorectal carcinoma cells after irradiation. Inhibition of *HOTAIR* expression, overexpression of miR-93 or silencing of ATG12 have remarkable effects on cell viability, apoptosis induction, inhibition of autophagy and enhancement of radiosensitivity of CRC cells. This suggests that *HOTAIR* downregulates miR-93, which upregulates *ATG12* and thus promotes radioresistance of CRC cells [251].

In CC, upregulation of *HOTAIR* enhances radioresistance and leads to entry into S phase. However, this effect is reversed by the overexpression of *P21*. This suggests that *HOTAIR* plays a role in regulating the susceptibility of cervical cancer cells through its interaction with *P21* [252]. In another study, HeLa and C33A cells showed much higher expression of *HOTAIR* than normal cervical cells. However, after irradiation, *HOTAIR* expression gradually decreased, leading to a decrease in viability and an increase in apoptosis of CC cells [253]. Interestingly, this effect could be compensated for an overexpression of *HOTAIR*. Further studies revealed that *HOTAIR* is involved in the regulation of radiosensitivity of CC cells and correlates with HIF-1α expression. On the other hand, suppression of *HOTAIR* in CC cells increased their sensitivity to radiation. This was achieved by upregulation of *miR-217* and downregulation of *HIF-1α* [253]. In PDAC, *HOTAIR* plays an oncogenic role and its expression is significantly increased in cell lines and tissues. Silencing *HOTAIR* increases the expression of Wnt inhibitor 1 (*WIF1*), which inhibits the Wnt/b-catenin signaling pathway. As a result, the expression of the EMT-related protein b-catenin decreases, leading to increased radiosensitivity and increased cell apoptosis after radiotherapy in PDAC cells [254].

Prospects

With studies showing increased *HOTAIR* expression in a variety of tumors and cell lines, there is increasing evidence that *HOTAIR* functions as an oncogenic driver in a variety of malignancies. It is not yet known which transcriptional networks and upstream signals drive this overexpression, but this could lead to the discovery

of new treatment targets. *HOTAIR*'s unique property lies in its dual molecular scaffold function, enabling simultaneous histone methylation and demethylation to reprogram chromatin states and silence tumor suppressor genes. Additionally, *HOTAIR* interacts with numerous pathways involved in carcinogenesis, amplifying its role in cancer progression, EMT, and chemoresistance. HOTAIR's extensive interactions with miRNAs and other lncRNAs enable it to function as a competitive endogenous RNA (ceRNA), and its consistent association with poor prognosis and recurrence across various cancer types establishes it as a versatile and impactful pan-cancer biomarker [255]. Further research into *HOTAIR*'s molecular signaling pathways is needed to realize its clinical potential. *HOTAIR* has significant prognostic value in gliomas, including lower grade tumors, highlighting its potential as a biomarker for stratifying patients based on molecular features that could serve as a basis for treatment decisions [256]. The simultaneous expression of *HOTAIR* and *HOXA9* in gliomas, but not in other cancers, suggests a unique regulatory mechanism in these tumors [167].

Targeting *HOTAIR* in vivo employs various innovative strategies aimed at reducing its expression or disrupting its function to counteract cancer progression. Antisense oligonucleotides (ASOs), synthetic nucleotide strands designed to bind specifically to *HOTAIR* RNA, facilitate its degradation or inhibition [199]. A notable study utilized a technetium-99m-labeled ASO probe encapsulated in liposomes, enabling in vivo imaging of *HOTAIR* expression in malignant glioma xenografts while showcasing therapeutic potential [199]. Peptide nucleic acids (PNAs), synthetic polymers mimicking DNA or RNA, have also been effective; for example, PNA3 disrupts the interaction between *HOTAIR* and the PRC2 subunit EZH2, significantly reducing tumor initiation and stem cell frequency in ovarian cancer models when combined with DNA methyltransferase inhibitors [144]. RNA interference (RNAi) methods using small interfering RNAs (siRNAs) precisely target and degrade *HOTAIR*, suppressing cancer proliferation and metastasis [257]. Similarly, CRISPR-Cas9 technology enables precise genome editing to disrupt the *HOTAIR* gene locus, effectively blocking its transcription and oncogenic activity [258]. Small molecule inhibitors that interfere with *HOTAIR*'s interaction with protein complexes like PRC2 represent another promising approach, as they inhibit its ability to epigenetically modulate gene expression [259]. Together, these strategies highlight the therapeutic potential of targeting *HOTAIR* in combating cancer.

Ongoing research on the role of *HOTAIR* in resistance to cancer therapies continues to evolve, presenting several challenges. While the association between *HOTAIR* and chemotherapy resistance is well known, studies often focus on a narrow range of drugs and cancer types, necessitating broader research. Large cohort studies are needed to investigate the association between *HOTAIR* polymorphisms and chemotherapy response [260]. Although the role of *HOTAIR* in promoting cancer progression through interactions with miRNAs and various signaling pathways is recognized [261], the complexity of these mechanisms and the variability of *HOTAIR*'s role in different cancer types make targeted therapy difficult [260]. Additionally, few studies have explored methods to reduce *HOTAIR* expression to alleviate drug resistance clinically, and the effective delivery of *HOTAIR*-targeted treatments requires precise targeting to avoid off-target effects. Addressing these challenges through comprehensive and targeted research could enhance our understanding and treatment of chemotherapy-resistant malignancies.

The knockdown of *HOTAIR* can reverse its oncogenic effects and halt tumor progression. *HOTAIR* interacts with miRNAs and regulates substrate mRNAs according to the ceRNA theory, suggesting that interventions in these networks could innovate cancer treatment [262]. In vitro studies have shown that certain anticancer drugs, bioactive molecules and *HOTAIR*-EZH2 inhibitors can decrease the expression of *HOTAIR* or interfere with its interaction with the PRC2 complex, resulting in an anti-tumor effect [263]. In addition, *HOTAIR* plays a crucial role in the regulation of immunotherapy, which has made significant progress in combined with chemotherapy. However, *HOTAIR* can also suppress immune responses and promote immune escape, which reduces the efficacy of immunotherapy and leads to poor prognosis. Further research is essential to understand and overcome these challenges, which could lead to more effective and personalized cancer treatments [238].

HOTAIR-targeted therapies in cancer treatment show promise but come with significant challenges due to their complex role in gene regulation and systemic effects. These therapies can cause off-target effects by disrupting normal gene expression, leading to unintended activation or suppression of genes, and impacting normal tissues where *HOTAIR* is expressed [198]. Immune system activation, resulting in inflammation and potential autoimmunity, has been observed, along with tissue-specific toxicities, particularly in rapidly dividing cells [196]. Chemoresistance and compensatory pathway activation pose risks, especially in heterogeneous tumours, while systemic side effects from delivery mechanisms, such as liver toxicity and cardiovascular disturbances, further complicate their use [236]. Moreover, drug-drug interactions can exacerbate toxicity, as seen in combination therapies [264]. While

these treatments reduce tumor progression in cancers like breast, ovarian, and glioblastomas, they are often associated with localized inflammation, fatigue, and neuroinflammation [196]. Advanced delivery systems and precision medicine approaches are critical to mitigate these side effects, ensuring the therapeutic potential of *HOTAIR*-targeting strategies is balanced against their risks.

Future directions include comprehensive genomic studies to better understand the spectrum of *HOTAIR*-related SNPs, development of targeted therapies, and clinical trials to test these interventions. Additionally, combining *HOTAIR*-targeted treatments with existing therapies could enhance efficacy, while personalized medicine approaches could optimize treatment based on individual genetic profiles and *HOTAIR* expression levels [256]. Immunotherapy normalizes the tumor microenvironment, decreases hypoxia, mitigates acidosis and increases reactive oxygen species, which increases the tumor's sensitivity to radiotherapy. This synergy has significant implications for the development of combined therapies where optimal timing, dosing and biomarkers are critical to therapeutic outcomes [265]. However, the vascular normalization induced by immunotherapy is transient and requires careful planning to maximize efficacy and minimize damage. Despite the potential, it remains difficult to inhibit *HOTAIR* in cancer cells and to establish clinical guidelines for differentiating patients who will respond to radiotherapy [265]. Further research is essential to develop tumor-specific delivery mechanisms for targeted ncRNA therapies, understand the precise mechanisms of *HOTAIR*, validate lncRNAs as diagnostic markers, and develop advanced detection technologies for clinical practice. Overcoming these challenges could lead to more effective and personalized cancer therapies.

Conclusion

There is ample evidence for the critical role of *HOTAIR* in the development and progression of various cancers. Understanding its biological role in various cancers is essential for determining its efficacy as a diagnostic or predictive biomarker. The expression level of *HOTAIR* can serve as a potential prognostic factor and help identify cancer progression and tumor stage, but clinical studies are needed to establish it as a biomarker or therapeutic target. The evaluation of *HOTAIR* polymorphisms as predictive or therapeutic biomarkers requires further investigation. Insights into the functions of *HOTAIR* may lead to a deeper understanding of malignancies and aid in the development of therapeutic and prognostic biomarkers for cancer treatment. *HOTAIR* is also a promising therapeutic target to improve the sensitivity of cancer therapies by targeting its expression pathways. Despite advances in the understanding of lncRNAs, including *HOTAIR*, further research is needed to elucidate their role in cancer development, progression and metastasis. Biomarker-driven personalized cancer therapies have gained attention, and technologies have been developed to detect biomarkers that predict response to therapy.

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