Role of HOXA transcript antisense RNA myeloid-specific 1 in cancer (Review)

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Abstract. A newly recognized class of master regulators known as long non-coding RNAs (lncRNAs) has emerged as key modulators of cancer. Among them, HOXA transcript antisense RNA myeloid-specific 1 (HOTAIRM1) was initially identified in acute promyelocytic leukemia, where it resides within the HOXA gene cluster. The involvement of HOTAIRM1 has been indicated in the pathogenesis of multiple cancer types, including glioma, acute myeloid leukemia and osteosarcoma, has been well documented. HOTAIRM1 controls the growth, invasion and migration of tumors through different mechanisms and it is associated with the clinicopathological characteristics of patients with tumors. The present review describes the expression, function and molecular mechanism of HOTAIRM1 in different types of cancer and discusses the future obstacles in diagnosing and treating malignant tumors.

Contents

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Abbreviations: lncRNAs, long non-coding RNAs; HOTAIRM1, HOXA transcript antisense RNA myeloid-specific 1; AML, acute myeloid leukemia; OS, osteosarcoma; EC, endometrial cancer; EMT, epithelial-mesenchymal transition; TC, thyroid cancer; NSCLC, non-small cell lung cancer; OSCC, oral squamous cell carcinoma; PCa, prostate cancer; PDAC, pancreatic ductal adenocarcinoma; HCC, hepatocellular carcinoma; ADC, lung adenocarcinoma; GC, gastric cancer; CRC, colorectal cancer; PRC2, polycomb repressive complex 2; H3K27me3, lysine residue 27 of histone 3

Key words: lncRNA, HOTAIRM1, cancer, function, regulator

1. Introduction

Cancer is a multifactorial disease due to various causes and impacts, such as environmental factors, infectious agents, genetic alterations and epigenetic shifts (1,2). Advances in genetic research have not only elucidated the pathogenesis of several cancer types, such as acute myeloid leukemia (AML), non-small cell lung cancer (NSCLC) and prostate cancer (PCa), but have also directly contributed to the development of treatments (3-6). For example, imatinib is an effective treatment for leukemia caused by mutations in the breakpoint cluster region-Abelson, offering the possibility of long-term disease remission. Furthermore, <2% of the entire genome encode proteins, while the rest of the genetic material is composed of non-coding genes, which are key contributors to tumorigenesis among multiple cancer types, such as PCa and colorectal cancer (CRC) (7-9).

Transcripts >200 nucleotides in length and which have little or no ability to code for proteins are termed long non-coding RNAs (lncRNAs) (10,11). Previous studies identified that several dysregulated lncRNAs contribute to the development and progression of cancer types, working as oncogenes or tumor suppressors (12-15). HOTAIRM1 is a recently identified lncRNA located in the HOXA gene cluster on the human chromosome 7p15.2 (Fig. 1) (16). HOTAIRM1 was first identified as involved in the differentiation of granulocytes in the NB4 promyelocytic leukemia model (17). Since its identification, HOTAIRM1 has gained notable attention in cancer research (18-20).

The relevant studies in the present review were collected using PubMed (https://pubmed.ncbi.nlm.nih.gov) with a combination of the following terms: 'HOTAIRM1', 'cancer', 'tumor' and 'disease'. English-language publications from the past 10 years were selected. Two reviewers (YJ and XL) independently performed an initial screening of titles and abstracts. The reference lists of potentially eligible articles were cross-checked to ensure extensive coverage of the literature. A total of 103 articles meeting the predefined literature searching criteria were identified by May 2025.

Therefore, the present review provides a comprehensive overview of the current understanding of the expression, roles and molecular mechanisms of HOTAIRM1 to regulate cancer.

2. HOTAIRM1 expression in cancer

Several previous studies have documented the abnormal expression of lncRNAs in different diseases, particularly in cancer (21-23). The dysregulation of lncRNAs contributes to the development of tumors through the promotion, proliferation, invasion and metastasis of cancer cells (24-26). The lncRNA HOTAIRM1 is upregulated in different types of cancer such as glioma (27-35), AML (36-38), osteosarcoma (OS) (39), endometrial cancer (EC) (40), thyroid cancer (TC) (41,42), NSCLC (43,44), oral squamous cell carcinoma (OSCC) (45), PCa (46), pancreatic ductal adenocarcinoma (PDAC) (47,48) and ovarian cancer (OC) (49,50). The involvement of HOTAIRM1 in governing tumor characteristics, including proliferation, invasion and metastasis, has been demonstrated. However, HOTAIRM1 expression is downregulated in papillary TC (PTC) (51), head and neck tumor (HNT) (52), hepatocellular carcinoma (HCC) (53), lung adenocarcinoma (ADC) (54), gastric cancer (GC) (55,56) and CRC (Table I) (57,58). These collective findings position HOTAIRM1 as a key tumor-related lncRNA, whose dysregulation could drive oncogenic pathways and offers a promising target for future cancer interventions.

HOTAIRM1 expression in glioma. Glioma is the most common primary central nervous system tumor (59). Several previous studies have reported a notable increase in HOTAIRM1 expression in glioblastoma tissues and cell lines when compared with their normal counterparts (27-32). Glioblastoma tissues and cells exhibit an abnormal HOTAIRM1 upregulation, which promotes glioma malignancy by enhancing cell proliferation, migration, invasion and VM formation. The high HOTAIRM1 expression is mediated by METTL3-dependent m^6A modification (33). Furthermore, Snail family transcriptional repressor 2 transcriptionally activated HOTAIRM1 and a strong association was observed between increased HOTAIRM1 expression and worse prognosis in glioma (34). HOTAIRM1 is also strongly associated with decreased survival rates of patients diagnosed with glioblastoma (35).

HOTAIRM1 expression in AML. AML is a heterogeneous disease characterized by genetic irregularities (including mutations in genes like FLT3, NPM1 and RUNX1) and epigenetic alterations (such as mutations in regulators of DNA methylation like DNMT3A, TET2 and IDH1/2) (60,61). Jing *et al* (36) observed that HOTAIRM1 expression was increased in 14 AML samples with nucleophosmin 1 (NPM1) mutations when compared with AML samples without NPM1 mutations. This finding suggested a potential functional link between HOTAIRM1 and this specific genetic irregularity, implying that HOTAIRM1 upregulation may be part of the oncogenic machinery in NPM1-mutated AML. Furthermore, Kaplan-Meier survival analysis on patients with AML demonstrated a notably reduced survival time in the group with high HOTAIRM1 expression. A different investigation demonstrated that the treatment of acute promyelocytic leukemia cells with all-trans retinoic acid led to an increase in HOTAIRM1 expression, which is key to myeloid differentiation. Notably, the transcription factor PU.1 binds to a specific DNA site (+1,100) in the promoter of the HOTAIRM1 gene, therefore activating it and increasing its expression (37). Furthermore, Hu *et al* (38) demonstrated that HOTAIRM1 expression is increased in patients with AML compared with individuals without the disease. The functional analysis indicated that HOTAIRM1 downregulation inhibits the growth and triggers cell death in AML cells, indicating its tumorigenic function in AML.

HOTAIRM1 expression in OS. OS is a prevalent and aggressive form of primary bone cancer that mostly affects children and teenagers (62). HOTAIRM1 expression is markedly increased in both OS samples and cell lines compared with their non-cancerous counterparts. The association between HOTAIRM1 expression and the clinicopathological features of patients with OS revealed that individuals with high HOTAIRM1 expression are prone to having an advanced TNM stage (as defined by the American Joint Committee on Cancer, 8th edition) (63). HOTAIRM1 upregulation stimulates the growth and movement of cells while inhibiting cell death. These findings suggest that HOTAIRM1, a cancer-causing gene in OS, potentially holds promise in the identification and management of this disease (39).

HOTAIRM1 expression in EC. In the female reproductive system, EC ranks as one of the top three prevalent malignancies (64). Li *et al* (40) identified markedly higher HOTAIRM1 expression in type I EC tissues compared with normal endometrium tissues and showed it is associated with the clinicopathological features of affected patients. The increased expression of HOTAIRM1 is also strongly associated with advanced International Federation of Gynecology and Obstetrics (FIGO) stage (according to the FIGO staging system, 2023 edition) (65) and the presence of lymph node metastasis. The suppression of HOTAIRM1 inhibits the growth, movement, infiltration of type I EC cells, epithelial-mesenchymal transition (EMT) and tumor growth *in vivo* (40).

HOTAIRM1 expression in TC. TC is divided into three main histological groups: i) Differentiated TC, which includes papillary, follicular and oncocytic carcinomas; ii) medullary TC, often associated with multiple endocrine neoplasia type 2 syndrome; and iii) anaplastic TC, an aggressive malignancy that often arises from pre-existing differentiated lesions and is characterized by a high mortality rate (66,67). Zhang *et al* (41) reported that HOTAIRM1 gene is amplified and its expression is increased in anaplastic TC compared with PTC and normal thyroid tissue. Furthermore, patients with anaplastic TC indicating higher HOTAIRM1 copy number and expression have worse survival outcomes. The role of HOTAIRM1 in TC appears to be complex and potentially context-dependent. While one study by Li *et al* (42) reported that elevated HOTAIRM1 expression in TC cells and tissues was associated with advanced TNM stage and lymph node metastasis, another investigation found contrary evidence, demonstrating that HOTAIRM1 expression was notably reduced in PTC tissues and that lower levels

Table I. HOTAIRM1 expression in several cancer types.

Cancer type	Expression	Functions	Associated genes	Role	(Refs.)
Glioma	Up	Migration, invasion, VM formation, proliferation, stemness and radiosensitivity	IGFBP2, FUS, HOXAs, miR-133b-3p, miR-137, miR-153-5p and TGM2	Oncogene	(27-35)
AML	Up	Autophagy, proliferation, apoptosis, cell cycle and differentiation	EGR1, miR-152-3p and miR-148b	Oncogene	(36-38)
OS	Up	Proliferation, apoptosis	miR-664b-3p	Oncogene	(39)
EC	Up	Proliferation, migration, invasion and EMT	HOXA1	Oncogene	(40)
TC	Up	Proliferation, apoptosis, migration and invasion	ILF3, pri-miR-144 and miR148a	Oncogene	(41,42)
NSCLC	Up	Proliferation, apoptosis, migration, invasion and glycolysis metabolism	miR-498	Oncogene	(43,44)
OSCC	Up	Proliferation and cell cycle	PCNA, cyclin D1, p53, p21, CDK4 and CDK6	Oncogene	(45)
PCa	Up	Proliferation and apoptosis	β-catenin	Oncogene	(46)
PDAC	Up	Proliferation, apoptosis, cell cycle and migration	CDK1, cyclin D1, p21, Bax, Bad and Bcl-2	Oncogene	(47,48)
OC	Up	Proliferation and apoptosis	MMP2	Oncogene	(49)
PTC	Down	Proliferation, migration and invasion	miR-107	Anticancer	(51)
OC	Down	Proliferation invasion and apoptosis	miR-106a-5p	Anticancer	(50)
HNT	Down	Proliferation, apoptosis, migration and invasion	miR-148a	Anticancer	(52)
HCC	Down	Proliferation and apoptosis	β-catenin	Anticancer	(53)
ADC	Down	Cell cycle, proliferation and invasion	miR-498	Anticancer	(54)
GC	Down	Proliferation, migration and apoptosis	miR-29b-1-5p and miR-17-5p	Anticancer	(55,56)
CRC	Down	Invasion, migration and multi-drug resistance	miR-17-5p	Anticancer	(57,58)

HOTAIRM1, HOXA transcript antisense RNA myeloid-specific 1; AML, acute myeloid leukemia; OS, osteosarcoma; EC, endometrial cancer; TC, thyroid cancer; NSCLC, non-small cell lung cancer; OSCC, oral squamous cell carcinoma; PCa, prostate cancer; PDAC, pancreatic ductal adenocarcinoma; OC, ovarian cancer; PTC, papillary thyroid cancer; HNT, head and neck tumor; HCC, hepatocellular carcinoma; ADC, lung adenocarcinoma; GC, gastric cancer; CRC, colorectal cancer; miR, microRNA; IGFBP2, insulin-like growth factor binding protein 2; HOXA1, homeobox A1; EGR1, early growth response 1; PCNA, proliferating cell nuclear antigen; ILF3, IL enhancer binding factor 3; FUS, fused in sarcoma; TGM2, transglutaminase 2; EMT, epithelial-mesenchymal transition; VM, vasculogenic mimicry.

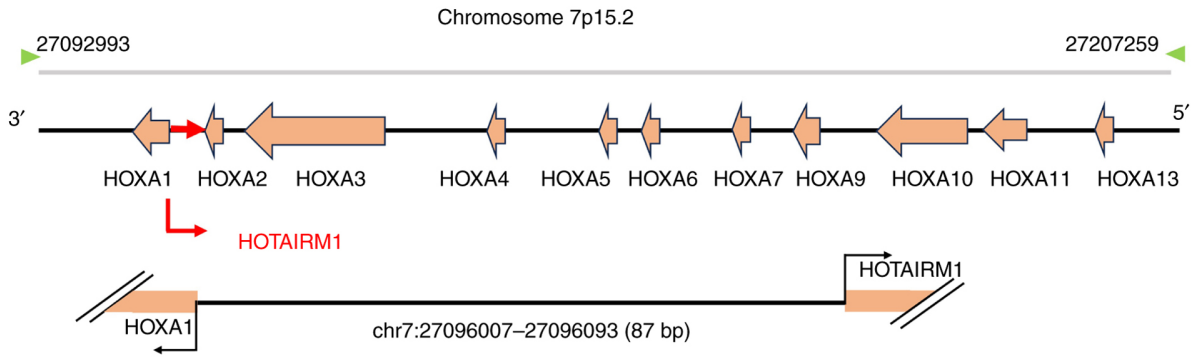

Figure 1. Schematic diagram of HOTAIRM1. HOTAIRM1, a long non-coding RNA located between HOXA1 and HOXA2, on the human chromosome 7p15.2. Arrows indicate transcription direction: Black for HOXA genes; red for the HOTAIRM1 transcript. HOTAIRM1, HOXA transcript antisense RNA myeloid-specific 1; chr, chromosome; HOX, homeobox.

correlated with lymph node metastasis and more advanced disease (51). This discrepancy highlights the need for further research to clarify the precise function of HOTAIRM1 in TC progression.

HOTAIRM1 expression in NSCLC. NSCLC is responsible for ~85% of cancer-related mortality globally, making it the primary contributor to lung cancer mortalities worldwide (68). Chen *et al* (43) observed that HOTAIRM1 expression is markedly increased in NSCLC tissues compared with tissues of a control group. A different study demonstrated that HOTAIRM1 expression is associated with tumor histological differentiation, tumor size, TNM stage and Ki-67 expression in patients with NSCLC. Furthermore, HOTAIRM1 expression is increased in NSCLC compared with that in adjacent non-cancerous tissues. Patients with NSCLC with low HOTAIRM1 expression have a markedly longer overall survival compared with those with high expression (44).

HOTAIRM1 expression in OSCC. OSCC is a malignant tumor with the highest occurrence rate among tumors affecting mouth and face. OSCC is well known for its tendency to recur and spread to other parts of the body (69,70). Yu *et al* (45) reported that HOTAIRM1 expression is increased in OSCC and it is closely associated with poor prognosis. Systematic bioinformatics analyses revealed that HOTAIRM1 is associated with tumor stage, overall survival, genomic instability, tumor cell stemness, tumor microenvironment activity and immunocyte infiltration.

HOTAIRM1 expression in PCa. PCa is a major contributor to cancer-associated mortality among men, particularly in Western countries, with Africa and Asia having the lowest incidence rates (71,72). Wang *et al* (46) reported that HOTAIRM1 expression is increased in PCa cells. The inhibition of HOTAIRM1 expression prevents tumor cell proliferation while inducing programmed cell death through the modulation of proteins associated with apoptosis. The inhibition of HOTAIRM1 expression limits the activity of the Wnt pathway in PCa cells, thereby suppressing the malignant characteristics of tumor cells.

HOTAIRM1 expression in PDAC. PDAC is the most common form of PCa arising from the epithelial lining of the pancreatic duct (73). Samples of 47 PDAC tissues and 5 cell lines exhibit an abnormal increase of HOTAIRM1 expression compared with its expression in a control group (47). Similarly, Zhou *et al* (48) reported that HOTAIRM1 expression is increased in 12 PDAC tissue samples when compared with the corresponding non-tumor samples.

HOTAIRM1 expression in OC. OC is the eighth most common type of cancer among women worldwide and is the third most frequent gynecological cancer after cervical cancer and EC (74). Ye *et al* (49) reported an overexpression of HOTAIRM1 in the human ovarian cancer cell line SKOV3. Inhibition of HOTAIRM1 expression reduces cell proliferation and increases cell death. Chao *et al* (50) observed that HOTAIRM1 expression is reduced in both ovarian cancer tissues and cells and advanced FIGO stage and lymphatic metastasis are associated with reduced HOTAIRM1 expression. HOTAIRM1 overexpression inhibits the growth and invasion of OC cells, while enhancing apoptosis. Furthermore, HOTAIRM1 slows OC tumor growth *in vivo*.

HOTAIRM1 expression in head and neck cancer. Head and neck cancer is a frequently diagnosed form of cancer globally, with an annual incidence of >600,000 new cases (75,76). Zheng *et al* (52) reported that HOTAIRM1 expression is decreased in 43 head carcinoma tissues and 41 neck carcinoma tissues when compared with the corresponding adjacent normal tissues. Furthermore, no association was identified between HOTAIRM1 expression and age, sex or tumor location. However, patients with increased HOTAIRM1 expression have a higher probability to develop an advanced TNM stage, suggesting that although HOTAIRM1 is generally downregulated in head and neck cancer, tumors that maintain a relatively higher expression (although still lower compared with normal tissues) are associated with increased malignancy and progression.

HOTAIRM1 expression in HCC. HCC is classified as the sixth most prevalent tumor and the third main reason of cancer fatality (77). Zhang *et al* (53) reported that HOTAIRM1 expression is lower in HCC tissues compared with that in the adjacent non-cancerous tissues. Furthermore, the receiver operating characteristic curve demonstrated that HOTAIRM1 expression so a notable level of sensitivity and specificity in detecting HCC. The absence of disease progression in patients with HCC is associated with tumor size and HOTAIRM1 expression. However, no association was observed with age, sex, γ-glutamyl transferase levels, α-fetoprotein levels, Child-Pugh grade (as defined by the American Association for the Study of Liver Diseases practice guidelines) (78), hepatitis B surface antigen status, presence of cirrhosis, number of tumors, micro-vessel metastasis, tumor differentiation and TNM stage of HCC.

HOTAIRM1 expression in ADC. Among NSCLCs, ADC is one of the key histological subtypes with high incidence and mortality (79,80). Thus, current studies on HOTAIRM1 primarily focus on ADC rather than other NSCLC subtypes, such as squamous cell carcinoma or large cell carcinoma. Chen *et al* (54) reported a notable decrease in HOTAIRM1 expression in ADC tissues compared with that in normal lung tissues. A clear association exists between the decrease of HOTAIRM1 expression and clinical stage, metastasis to lymph nodes and tumor size. Furthermore, HOTAIRM1 inhibition is associated with poor overall survival in patients with ADC, as demonstrated by the Kaplan-Meier analysis.

HOTAIRM1 expression in GC. GC is a prevalent malignancy worldwide. GC ranks as the second most prevalent form of cancer in China and ranks as the third leading cause of cancer-associated mortality (81). Xu *et al* (55) identified a notable decrease of HOTAIRM1 expression in GC tissues is associated with a low survival rate among patients with GC. These findings are consistent with those reported by Lu *et al* (56) suggesting a marked decrease in HOTAIRM1 expression in 20 gastric cancer tissues and cell lines. Furthermore, HOTAIRM1 expression is associated with the clinicopathological features of patients with GC and a strong association exists between decreased HOTAIRM1 expression and advanced TNM stage as well as lymph node metastasis.

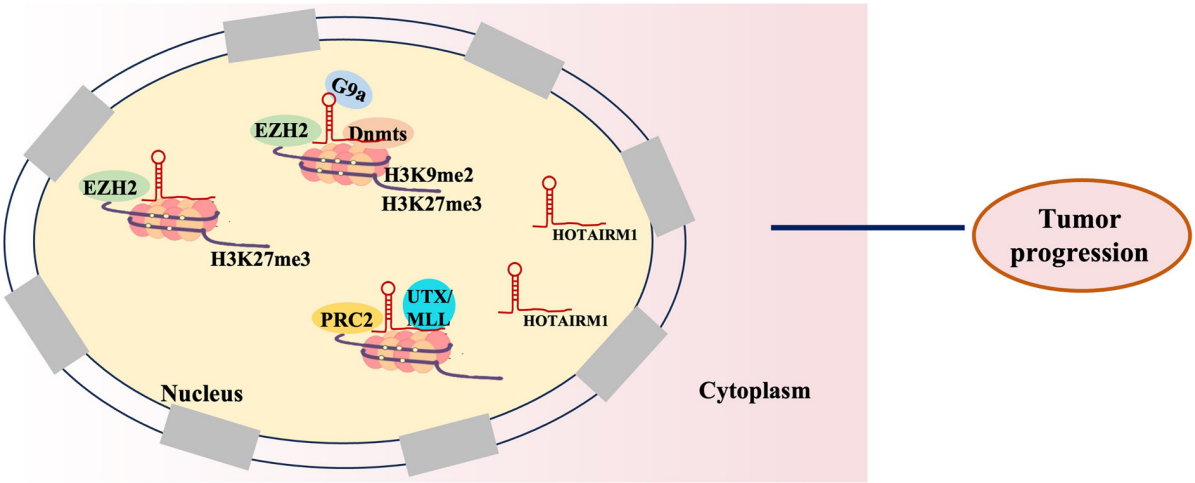

Figure 2. HOTAIRM1 interaction with DNA to exert a regulatory role in tumor progression. Interaction with PRC2/EZH2: HOTAIRM1 directly interacts with EZH2 of the PRC2 complex, preventing the deposition of the repressive H3K27me3 mark at target gene promoters; Interaction with H3K9 methyltransferases and DNMTs: HOTAIRM1 binds to and prevents the recruitment of H3K9 methyltransferases and DNA methyltransferases to promoters, thereby reducing repressive H3K9me2 and DNA methylation. Interaction with histone demethylases: HOTAIRM1 interacts with histone demethylases to help control chromatin structure and activate transcription of target gene cluster. HOTAIRM1, HOXA transcript antisense RNA myeloid-specific 1; EZH2, enhancer of zeste homolog 2; H3K27me3, lysine residue 27 of histone 3; H3K9me2, histone H3 lysine 9 dimethylation; UTX, ubiquitously transcribed tetratricopeptide repeat on chromosome X; MLL, mixed lineage leukemia; PRC2, polycomb repressive complex 2; G9a, euchromatic histone-lysine N-methyltransferase 2.

HOTAIRM1 expression in CRC. CRC is one of the most prevalent malignancies worldwide, with particularly high incidence in Western countries (82,83). Wan *et al* (57) reported that HOTAIRM1 expression is reduced in CRC tissues compared with that in normal tissues. Furthermore, in the matched cohort, plasma HOTAIRM1 levels were markedly lower in patients with CRC compared with those in healthy controls. Ren *et al* (58) identified a similar scenario where HOTAIRM1 expression is downregulated in both CRC tissues and cell lines and is even lower in 5-fluorouracil (FU)-resistant CRC tissues and cell lines. This progressive downregulation in resistant tissues and cell lines strongly implied that the loss of HOTAIRM1 is a key event in the acquisition of chemoresistance, consistent with its established role in suppressing cancer progression through mechanisms such as the miR-17-5p/BTG3 axis (58).

3. Mechanisms involved in the regulation of HOTAIRM1

LncRNAs interact with DNA, RNA or proteins as molecular absorbers, frameworks and stimulators, exerting regulatory functions in different biological processes, including gene regulation, cellular differentiation and human diseases, particularly cancer (84-88). HOTAIRM1 is involved in normal and abnormal biological processes. Several molecular functions have been identified after years of research and they are categorized into three primary pathways: i) Interaction with DNA; ii) interaction with RNA; and iii) interaction with proteins.

Interaction with DNA. HOTAIRM1 is involved in the methylation alteration of several genes that are associated with tumors and in the modification of histones (Fig. 2). HOTAIRM1 controls gene expression through its interaction with polycomb repressive complex 2 (PRC2), which consists of enhancer of zeste homolog 2 (EZH2), suppressor of zeste 12 homolog and embryonic ectoderm development protein. HOTAIRM1 catalyzes the dimethylation and trimethylation of the histone 3 lysine residue 27 (H3K27me3), thus controlling the expression of its gene. Li *et al* (89) identified that HOTAIRM1 triggers the transcription of the homeobox A1 (HOXA1) gene by reducing the levels of histone H3 lysine 9 (H3K9) dimethylation, H3K27me3 and DNA methylation, which are markers associated with the suppression of gene expression. HOTAIRM1 prevents the recruitment of histone H3K9 methyltransferase, EZH2 and DNA methyltransferases to the HOXA1 promoter during its interaction with them, thereby reducing their local abundance at this site (89). Kim *et al* (90) reported that HOTAIRM1 directly interacts with EZH2, the histone methyltransferases responsible for H3K27me3 trimethylation, thereby preventing the deposition of H3K27me3 marks at the putative HOXA1 promoter. Therefore, HOXA1 expression is increased in ER^+ breast cancer cells. Furthermore, HOTAIRM1 interacts with the histone demethylases PRC2 and ubiquitously transcribed tetratricopeptide repeat on chromosome X/mixed lineage leukemia to control chromatin structure and subsequently impacts the transcriptional activity of the HOXA gene cluster (91).

Interaction with RNA. HOTAIRM1 also interacts with RNA to mediate several molecular functions, including the promotion of cell proliferation (33,36), invasion and metastasis (40,58). The relevance of competitive endogenous RNA (ceRNA) networks in cancer initiation and progression has become apparent in recent years (92,93). MicroRNAs (miR/miRNA) are involved in the ceRNA network, exerting a negative influence on mRNA expression. The canonical mechanism involves miRNAs binding to the 3'-untranslated regions of target mRNAs, which leads to their demethylation and subsequent destabilization (94,95). HOTAIRM1 competitively binds to specific miRNAs through the ceRNA mechanism, thereby relieving the repression of their

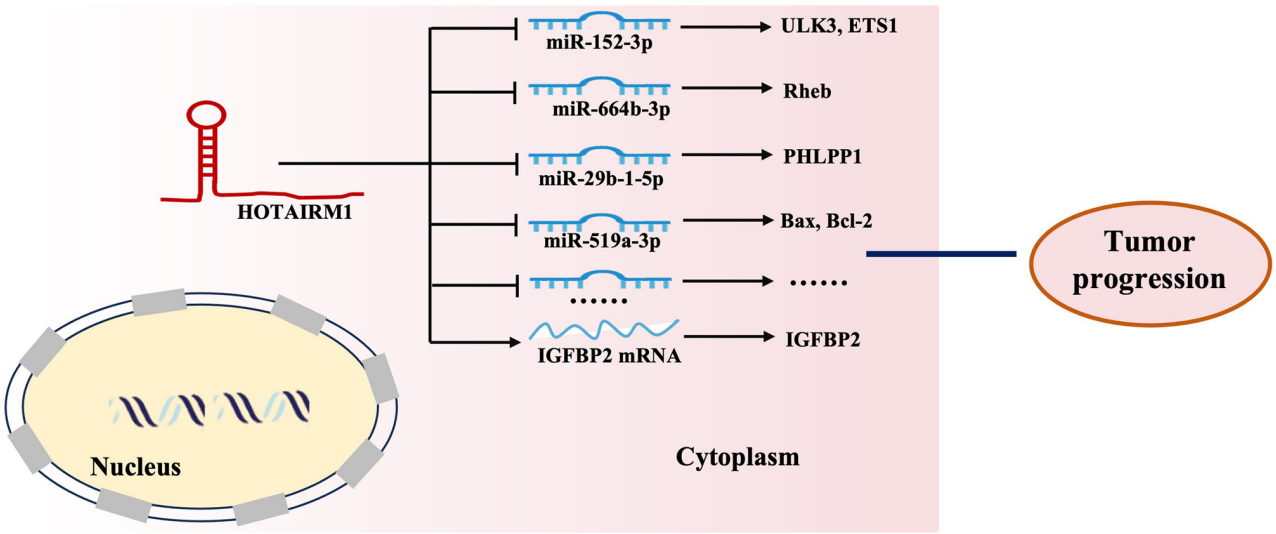

Figure 3. HOTAIRM1 interaction with RNA to exert a regulatory role in tumor progression. Interaction with specific miRNAs (e.g., miR-152-3p, miR-664b-3p, miR-29b-1-5p, miR-519a-3p): HOTAIRM1 functions as a competitive endogenous RNA or 'molecular sponge' by binding to these miRNAs, leading to the upregulation of genes like ULK3, ETS1, Rheb, PHLPP1, Bax, and Bcl-2, which in turn modulates tumor progression. Interaction with IGFBP2 mRNA: HOTAIRM1 directly binds to IGFBP2 mRNA to promote tumor progression. HOTAIRM1, HOXA transcript antisense RNA myeloid-specific 1; miR, microRNA; ULK3, Unc-51 like kinase 3; ETS1, E26 transformation-specific 1; Rheb, Ras homolog enriched in brain; PHLPP1, PH domain leucine-rich repeat protein phosphatase 1; IGFBP2, insulin-like growth factor binding protein 2.

target mRNAs and modulating tumor progression (Fig. 3). HOTAIRM1 competitively binds to miR-152-3p, functioning as a ceRNA that inhibits miR-152-3p activity and therefore upregulates its target Unc-51 like kinase 3 (ULK3), thereby modulating various leukemic cell processes, including autophagy, proliferation and apoptosis (36). Yu *et al* (39) identified that HOTAIRM1 functions as a molecular sponge for miR-664b-3p, thereby upregulating Ras homolog enriched in brain (Rheb) and activating the mTOR pathway to promote the Warburg effect in OS. Furthermore, it enhances E26 transformation-specific 1 (ETS1) mRNA expression and facilitates the osteogenic differentiation of mesenchymal stem cells derived from human bone marrow (96). Similarly, HOTAIRM1 promotes PH domain leucine-rich repeat protein phosphatase 1 upregulation in GC cells by sponging miR-29b-1-5p, thus demonstrating a classic ceRNA mechanism (55). Wang *et al* (97) reported that the HOTAIRM1/miR-519a-3p axis is markedly involved in the proliferation, apoptosis, inflammation and oxidative stress of neuroblastoma cells when exposed to the toxic metabolite 1-methyl-4-phenylpyridinium. HOTAIRM1 directly regulates mRNA stability. Specifically, its binding to insulin-like growth factor binding protein 2 (IGFBP2) mRNA increases IGFBP2 expression, thus promoting glioma cell proliferation, migration, invasion and vasculogenic mimicry formation (27).

Interaction with proteins. Several lncRNAs including HOTAIRM1 are involved in the molecular regulation of proteins by directly binding to them (Fig. 4). For example, HOTAIRM1 interacts with heat shock protein family A (Hsp70) member 5 (HSPA5) and transcriptionally regulates its expression, with the resulting effects on proliferation being partly dependent on this chaperone (98). Han *et al* (98) demonstrated that HOTAIRM1 forms a complex with polypyrimidine tract-binding protein 1 and insulin-like growth factor 2 mRNA-binding protein 2, strengthening their interaction and facilitating their recruitment to the serine hydroxymethyltransferase 2 (SHMT2) mRNA. Therefore, the stability of SHMT2 mRNA has improved, leading to an increase in SHMT2 protein expression. This ultimately induces mitochondrial activity and promotes the malignant advancement of glioma. Liu *et al* (28) reported that HOTAIRM1 binds to the RNA-binding protein fused in sarcoma (FUS), thereby regulating E2F transcription factor 7 expression, promoting the proliferation, migration and invasion of glioma stem cell-transformed mesenchymal stem cells. In addition, Chen *et al* (99) demonstrated that the regulation of programmed cell death-ligand 1 expression in lung alveolar epithelial cells is controlled by HOTAIRM1 through its interaction with the key transcription factor HOXA1, having alleviated lung injury and improved survival of mice. Jing *et al* (36) demonstrated that the interaction of HOTAIRM1 with early growth response 1 (EGR1) and murine double minute 2 homolog (MDM2) suggests that it serves as a scaffold facilitating MDM2 recruitment to EGR1, thereby promoting autophagy and proliferation in leukemia cells.

4. HOTAIRM1 regulates various hallmarks of cancer

Cancer is complex disease characterized by multiple genetic abnormalities, including epigenetic alterations, chromosomal translocations and gene deletions or amplifications. The human genome encodes several lncRNAs (such as PVT1, HOTAIR and MALAT1), most of which are not translated into proteins. Despite their lack of coding potential, lncRNAs exert key regulatory functions among different cellular processes (11,100). Among them, HOTAIRM1 modulates multiple signaling pathways (Wnt, Caspase signaling pathways) and is associated

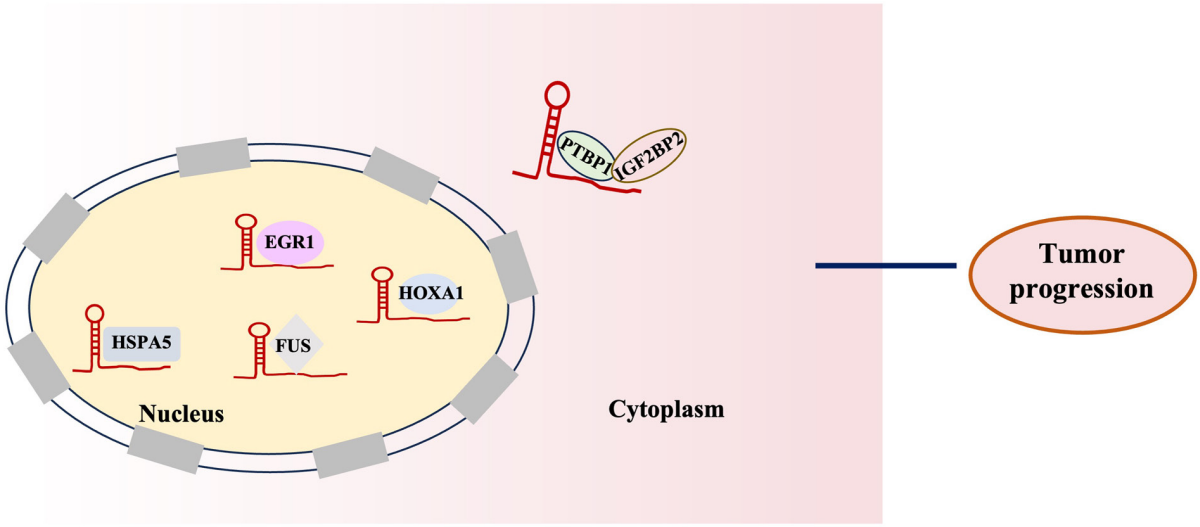

Figure 4. HOTAIRM1 interaction with proteins to exert a regulatory role in tumor progression. Interaction with HSPA5: HOTAIRM1 interacts with HSPA5 to transcriptionally regulate its expression, influencing tumor progression. Interaction with PTBP1 and IGF2BP2: HOTAIRM1 forms a complex with PTBP1 and IGF2BP2 to enhance its stability, thereby promoting tumor progression. Interaction with FUS: HOTAIRM1 binds to the RNA-binding protein FUS to promote tumor progression. Interaction with HOXA1: HOTAIRM1 interacts with HOXA1 to regulate tumor progression. Interaction with EGR1: HOTAIRM1 acts as a scaffold, facilitating the EGR1 to promote tumor progression. HOTAIRM1, HOXA transcript antisense RNA myeloid-specific 1; IGF2BP2, insulin-like growth factor 2 mRNA-binding protein 2; EGR1, early growth response 1; FUS, fused in sarcoma; HSPA2, heat shock protein family A (Hsp70) member 2; PTBP1, polypyrimidine tract-binding protein 1; HOXA1, homeobox A1.

with hallmark cancer traits such as cell proliferation, apoptosis, invasion, metastasis, metabolic reprogramming and angiogenesis (Fig. 5).

Proliferation. Dysregulated cell proliferation resulting in uncontrolled growth represents a fundamental hallmark of tumorigenesis (101). Aberrant expression of HOTAIRM1 has been reported in multiple tumor types and is closely associated with enhanced tumor cell proliferation. For example, Wu *et al* (33) identified an increase in HOTAIRM1 expression in both glioma tissues and cells. Furthermore, HOTAIRM1 overexpression increases the proliferation of glioma cells. Zhou *et al* (102) identified a key functional connection among HOXA4, HOTAIRM1 and HSPA5, forming a novel regulatory circuit that governs HUVEC proliferation. HOTAIRM1 promotes OS cell proliferation by sponging miR-664b-3p, thereby activating the mTOR pathway (39). On the other hand, HOTAIRM1 also suppresses the proliferative ability of granulosa cells (103). Furthermore, Jing *et al* (36) demonstrated that HOTAIRM1 markedly promotes the proliferation of AML cells harboring NPM1 mutations.

Cell death. Apoptosis is a programmed form of cell death that maintains cellular balance. The induction of apoptosis in cancer cells is a key strategy in clinical cancer therapy. Dahariya *et al* (104) reported that HOTAIRM1 functions as a molecular decoy for miR-125b regulating apoptosis to facilitate the terminal differentiation of megakaryocytes, thereby regulating key processes including apoptosis, cyclin D1-dependent cell cycling, and reactive oxygen species production. HOTAIRM1 also induces Jurkat cell apoptosis through the KIT/AKT signaling pathway (105). Liu *et al* (106) demonstrated that the loss of HOTAIRM1 activity causes an abnormal increase in chondrocyte apoptosis. Similarly, Ye *et al* (49) reported that HOTAIRM1 suppression increases the expression of pro-apoptotic factors, including Bad and Bax, while it reduces the expression of BH3 interacting-domain death agonist and Bcl-2 (anti-apoptotic factors) in ovarian cancer cells.

Autophagy is a self-degradative process in which cytoplasmic proteins and organelles are delivered to lysosomes to maintain cellular metabolism and homeostasis. A previous study has reported that HOTAIRM1 induces autophagy by upregulating ULK3 expression, leading to an increased expression of autophagy-related proteins including microtubule-associated protein LC3 II and a concomitant decrease in the autophagy substrate p62, thereby promoting cell proliferation and exerting a pro-tumorigenic effect (36).

Invasion and metastasis. Metastasis is a complex, multistep process involving EMT, invasion, intravasation, cell survival in the bloodstream, extravasation and the formation of secondary tumor colonies. The initial step in cancer metastasis is the EMT, during which epithelial cells lose their polarity and intercellular adhesion, acquire mesenchymal characteristics and gain enhanced migratory and invasive abilities. The upregulation of HOXA1 expression by HOTAIRM1 enhances the ability of type I EC cells to undergo EMT and metastasis, resulting in a decrease in the epithelial marker E-cadherin expression and an increase in the mesenchymal marker N-cadherin (40). Ren *et al* (58) examined the impact of HOTAIRM1 dysregulation in 5-FU-resistant CRC cells and identified that the increased expression of HOTAIRM1 reduces cell invasion and migration according to EMT assay.

Cell differentiation. Cell differentiation is the process through which cells acquire specialized function and form distinct tissues. By contrast, carcinogenesis represents a breakdown

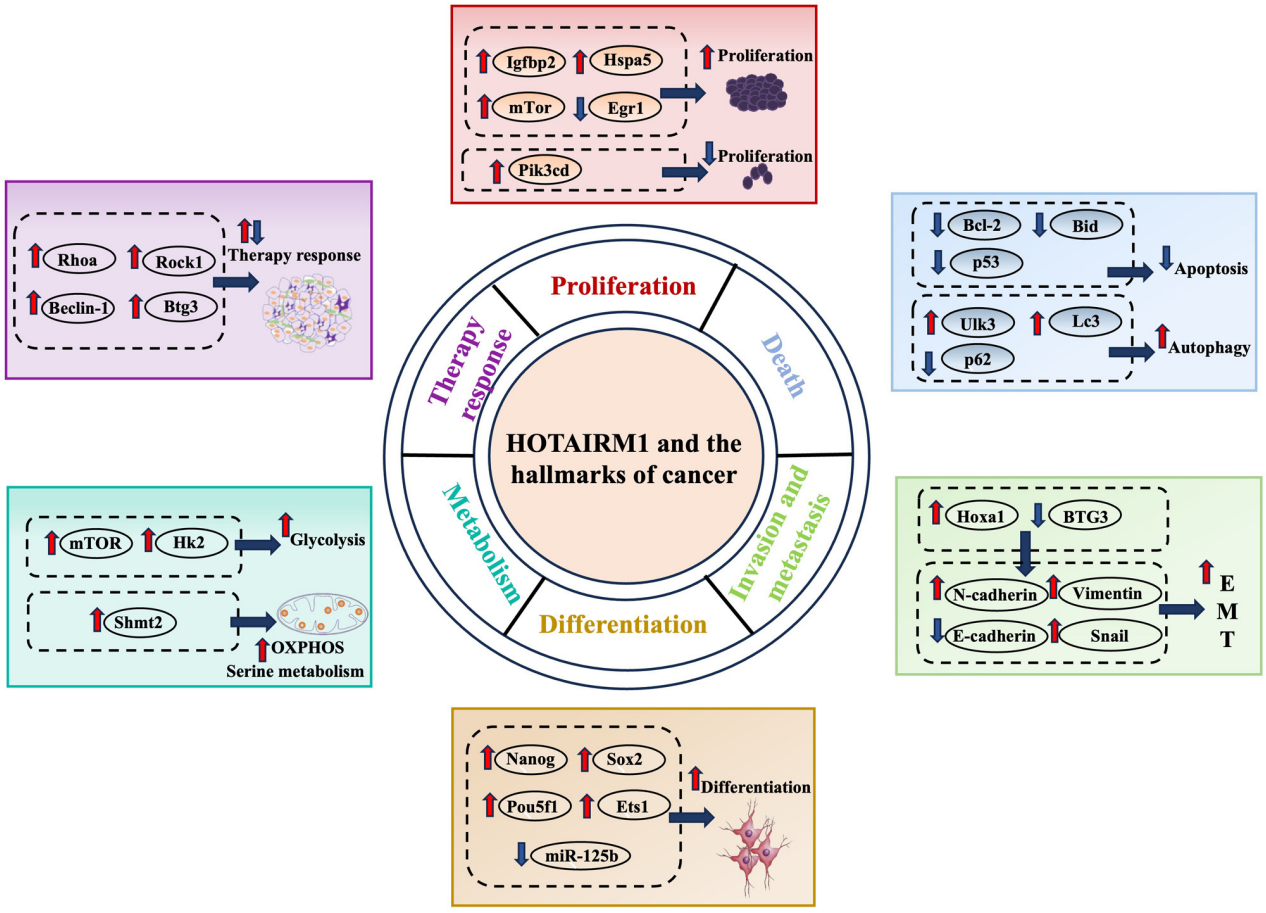

Figure 5. HOTAIRM1 regulates various hallmarks of cancer. HOTAIRM1 promotes cell proliferation by upregulating Igfbp2/Hspa5/mTor or downregulating Egr1, while also upregulating Pik3cd to exert an inhibitory effect on proliferation; HOTAIRM1 suppresses apoptosis by downregulating Bcl-2/Bid/p53 and promotes autophagy by upregulating Ulk3/LC3 while downregulating p62; HOTAIRM1 promotes EMT by upregulating Hoxa1 and downregulating BTG3, leading to increased N-cadherin/Vimentin/Snail and decreased E-cadherin; HOTAIRM1 promotes cell differentiation by upregulating Nanog/Sox2/Pou5f1/Ets1 and downregulating miR-125b; HOTAIRM1 promotes metabolic reprogramming by upregulating mTOR/Hk2 to enhance glycolysis and increasing Shmt2 to stimulate serine metabolism; HOTAIRM1 modulates therapy response through upregulating RhoA/ROCK1/Beclin-1/BTG3 expression. HOTAIRM1, HOXA transcript antisense RNA myeloid-specific 1; Igfbp2, insulin-like growth factor binding protein 2; Egr1, early growth response 1; miR, microRNA; Ulk3, Unc-51 like kinase 3; Hoxa1, homeobox A1; Ets1, E26 transformation-specific 1; Shmt2, serine hydroxymethyltransferase 2; Hk2, hexokinase 2; Btg3, B-cell translocation gene 3; Rock1, ρ-associated coiled-coil containing protein kinase 1; Rhoa, Ras homolog family member A; Bid, BH3 interacting-domain death agonist; Pik3cd, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit Δ.

of normal differentiation, resulting in the uncontrolled proliferation of immature or aberrant cells. Tollis *et al* (107) used a model framework of spinal motor neurons to demonstrate that neuronal HOTAIRM1, a specific isoform of HOTAIRM1, influences cell fate between motor neurons and interneurons by promoting motor neuron differentiation. HOTAIRM1 contributes to proper progression during the early stages of neuronal differentiation. It also influences the core pluripotency network composed of NANOG, POU class 5 homeobox 1 and Sox2, thereby helping to maintain cells in an undifferentiated state (108). Wang *et al* (73) identified HOTAIRM1 as a novel regulator of the osteogenic differentiation of bone marrow-derived mesenchymal stem cells. This regulation occurs through the miR-152-3p/ETS1 axis, suggesting that HOTAIRM1 may represent a potential therapeutic target for osteoporosis. Furthermore, Dahariya *et al* (104) demonstrated that HOTAIRM1 regulates the p53-mediated control of cyclin D1 expression during megakaryocytopoiesis. The function of HOTAIRM1 is to promote megakaryocyte maturation by acting as a molecular sponge for miR-125b.

Metabolism. Tumor cells undergo notable metabolic reprogramming to support their rapid proliferation. Unlike regular cells, they preferentially use aerobic glycolysis, an energetically inefficient pathway with a considerably higher turnover rate, even under oxygen-sufficient conditions, a phenomenon known as the Warburg effect. The miR-664b-3p/Rheb/mTOR axis markedly improves the Warburg effect in OS cells, due to the notable enhancement by HOTAIRM1 (39). HOTAIRM1 knockdown attenuates the Warburg effect in NSCLC by reducing glucose uptake and lactate production. This metabolic suppression is associated with a marked decrease in hexokinase 2 protein expression, a key glycolytic enzyme that phosphorylates glucose to initiate glycolysis and sustain cancer cell energy metabolism (43). Han *et al* (98) reported that HOTAIRM1 increases SHMT2 protein expression by improving the lifespan of its mRNA, leading to the stimulation of mitochondrial activity through oxidative phosphorylation and serine metabolism.

Therapy response. Despite notable advances in antitumor therapies, resistance to chemotherapy, radiotherapy, targeted

therapy and immunotherapy still represents a major obstacle to an effective cancer treatment (109). HOTAIRM1 is involved in the response to therapy by cancer cells. According to previous research, HOTAIRM1 interacts with the inhibitory region of ρ GTPase-activating protein 18 and suppresses its expression, resulting in the activation of the Ras homolog family member A/ρ-associated coiled-coil containing protein kinase 1 signaling pathway and enhancing leukemia cell resistance to glucocorticoid treatment (110). Gu *et al* (111) reported that HOTAIRM1 upregulation leads to lenvatinib resistance by reducing miR-34a expression and increasing Beclin-1 expression in HCC cancer cells. In addition, Chen *et al* (112) revealed that HOTAIRM1 suppression increases the effectiveness of cytarabine in killing cells by controlling the Wnt/β-catenin/platelet-type isoform of phosphofructokinase signaling pathway. *In vitro* and *in vivo*, HOTAIRM1 functions as a tumor suppressor in 5-FU-resistant CRC cells by reducing the activity of the miR-17-5p/B-cell translocation gene 3 (BTG3) pathway and preventing the development of multi-drug resistance (58).

5. Conclusion and prospects

Cancer remains a major global threat to human health. Although recent advances have slightly reduced the overall mortality rates, notable obstacles persist in the early diagnosis and effective management. Numerous patients are still diagnosed at advanced stages of the disease, which notably worsens their prognosis (113,114). Hence, it is key to identify novel biomarkers and examine the different molecular pathways involved in cancer for its timely detection and management.

Several studies have indicated the abnormal expression of lncRNAs in several diseases and their ability to function as tumor suppressors or oncogenes (115,116). HOTAIRM1 exhibits an abnormal expression in both tumor tissues and cells of different types of cancer and it serves as a standalone indicator for unfavorable prognosis in a wide range of carcinomas. HOTAIRM1 upregulation promotes tumor cell proliferation in several neoplasms, including glioma, AML, OS, EC, TC, NSCLC, OSCC, PCa, PDAC and OC. However, HOTAIRM1 upregulation suppresses cancer cell proliferation in PTC, OC, HNT, HCC, ADC, GC and CRC. Furthermore, a strong association exists between atypical HOTAIRM1 expression and several clinical and pathological characteristics of tumors, including age, tumor size, invasion of blood vessels, metastasis, overall survival and recurrence. These findings support the idea that the cellular function of HOTAIRM1 is not static but context-dependent.

Initially, HOTAIRM1 triggers H3K27me3 by interacting with EZH2/PRC2 and also participates in the alteration of chromatin structure by directing the recruitment of chromatin-modifying enzymes to a specific gene location. Furthermore, HOTAIRM1 acts as a molecular sponge for miRNAs, exerting its regulatory effects through the HOTAIRM1-miRNA-mRNA pathway. In addition, HOTAIRM1 binds to functional proteins within both the nucleus and cytoplasm, thereby modulating their expression and markedly influencing tumor progression. Other potential molecular mechanisms underlying the biological functions of HOTAIRM1 warrant further investigation.

HOTAIRM1 potentially regulates tumors and impacts multiple aspects of cancer, such as cell proliferation, death, invasion, spread, cellular differentiation, metabolism and resistance to chemotherapy. Nevertheless, in certain contexts, such as drug resistance, the exact function of HOTAIRM1 remains to be elucidated, as current studies report conflicting results that require further detailed investigation. Liang *et al* (110) revealed that HOTAIRM1 promotes GC resistance by inhibiting apoptosis in leukemia cells. Notably, Ren *et al* (58) reported that HOTAIRM1 suppresses the miR-17-5p/BTG3 pathway, leading to the inhibition of multi-drug resistance. Currently, further in-depth research is required to explore the potential ability of HOTAIRM1 to control additional characteristics of cancer, including the evasion of immune surveillance, genome instability and mutation, non-mutational epigenetic reprogramming, unlocking phenotypic plasticity and polymorphic microbiomes.

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Availability of data and materials

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Authors' contributions

YJ and YG conceptualized the present review. YJ and XL prepared the original draft. YJ and YG reviewed and edited the manuscript. YJ and YG provided supervision and project administration. YJ obtained funding for the present review. All authors read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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