REVIEW ARTICLE

The Diverse Roles of Long Non-Coding RNA HOTTIP in Breast and Gynecological Cancer Progression

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Abstract: Long non-coding RNAs (lncRNAs) play vital roles in the development and progression of various tumors through multiple mechanisms. Among these, HOTTIP (HOXA transcript at the distal tip) stands out as an intriguing candidate with diverse functions in several malignancies, including breast cancer and gynecologic cancers such as ovarian, cervical, and endometrial cancers, which are significant global health concerns. HOTTIP interacts with key signaling pathways associated with these cancers, including Wnt/β-catenin, PI3K/AKT, and MEK/ERK pathways, enhancing their activation and downstream effects. Its influence extends to crucial aspects of cancer biology, such as cell proliferation, apoptosis, migration, invasion, angiogenesis, and epithelial-mesenchymal transition (EMT). Additionally, HOTTIP plays a pivotal role in the pathogenesis of breast and gynecologic tumors by sponging various microRNAs (miRNAs) and regulating the expression of mRNAs involved in critical molecular processes. This dysregulation is often associated with poor clinical outcomes, advanced disease stages, and distant metastases. Understanding the functional roles of HOTTIP in these cancers is essential for developing targeted therapeutic strategies. This review aims to explore the emerging roles of HOTTIP in breast and gynecologic cancers.

Keywords: Gynecologic cancers, lncRNAs, HOTTIP, targeted therapy.

1. INTRODUCTION

Gynecologic cancers (GCs) encompass a heterogeneous group of malignancies that affect the female reproductive system [1, 2]. The most prevalent types of GCs include uterine (endometrial) cancer, originating in the endometrium or the lining of the uterus [3]; ovarian cancer, arising from the ovaries [4]; cervical cancer, developing in the cervix [5], vulvar cancer [6], and vaginal cancer, originating in the vaginal lining [7].

Breast cancer (BC) is one of the most common malignant tumors in females worldwide, characterized by high rates of metastasis, recurrence, and mortality [8]. Despite significant advancements in treatment strategies for different molecular subtypes of BC, many patients experience unsatisfactory therapeutic responses due to drug resistance [9]. This resistance often leads to low survival rates and poor prognoses [10].

The risk of developing GCs and BC escalates with advancing age [11]. A family history of GCs, especially ovarian and also BC, can heighten the susceptibility

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[12]. Inherited gene mutations, such as BRCA1 and BRCA2, are strongly associated with an elevated risk of ovarian and BCs [13, 14]. Certain strains of Human Papillomavirus (HPV) infection can also increase the likelihood of developing cervical and vaginal cancers [15]. Several factors can influence a woman's hormonal profile and, in turn, affect her risk of developing GCs. For instance, early onset of menstruation, late onset of menopause, and the use of hormone replacement therapy can all play significant roles in modulating this risk [16].

The management of cancer is influenced by several factors, including the specific type and stage of the disease, as well as the overall health and well-being of the affected woman [17]. options include a variety of approaches, such as surgical interventions like hysterectomy (removal of the uterus) [18], oophorectomy (removal of the ovaries) [19], and lymph node dissection [20]. Other therapeutic options include radiation therapy, which uses high-energy X-rays or other forms of radiation either externally or internally through brachytherapy [21]. Chemotherapy, administered either orally or intravenously, is another widely used treatment method [22]. Additionally, targeted therapies that specifically address molecular abnormalities in cancer cells have shown promising results [23, 24]. Hormone therapy [25] and various molecular approaches are also utilized in specific cases, depending on the individual patient's needs [26].

Recent scientific research has highlighted the important role of dysregulated long non-coding RNAs (lncRNAs) in the development of GCs and BC [8, 27, 28]. In particular, the lncRNA HOTTIP (HOXA transcript at the distal tip) has emerged as a significant contributor to these cancers [29, 30]. Elevated levels of HOTTIP have been associated with tumor growth, invasion, and metastasis in ovarian cancer [31]. Moreover, increased expression of HOTTIP has been found in endometrial cancer tissues compared to normal endometrial tissues [29]. This heightened expression correlates with advanced tumor stages, lymph node metastasis, and poorer prognosis [32]. HOTTIP is thought to function as an oncogenic lncRNA by interacting with various cellular pathways and epigenetic regulators [33]. This suggests that HOTTIP may contribute to the aberrant gene expression patterns observed in these cancers. In this study, we provide a comprehensive summary of the functional roles of HOTTIP in BC, ovarian, cervical, and endometrial cancers.

2. FUNCTIONAL ROLES OF LNCRNA HOTTIP IN HEALTH AND DISEASES

HOTTIP is transcribed from a genomic region located at the 5' end of the HOXA gene cluster on chromosome 7 [34]. Its transcription is facilitated by RNA polymerase II from a DNA region upstream of the HOXA gene cluster [35]. The expression of HOTTIP is regulated by various microRNAs (miRNAs) [36], which are small non-coding RNAs that can bind to target messenger RNAs (mRNAs) and modulate their translation or degradation [37]. HOTTIP plays essential functional roles in a wide range of biological processes associated with health and diseases [38]. It is involved in embryonic development and cellular differentiation [39], contributing to the regulation of gene expression in the HOXA gene cluster, which is critical for body pattern formation and organ development [40]. HOTTIP also influences the osteogenic differentiation of bone marrow mesenchymal stem cells (BMSCs) through the Wnt/β-catenin signaling pathway [41] and stimulates angiogenesis [42]. The involvement of HOTTIP in these diseases suggests its potential as a biomarker or therapeutic target.

3. THE ROLE OF HOTTIP IN THE PATHOGENESIS AND PROGRESSION OF GCs

The dysregulation of HOTTIP in GCs provides compelling evidence for its involvement in driving tumor formation and disease progression (Table **1** and Fig. **1**). Here, we have summarized the functional roles of this lncRNA in ovarian, BC, cervical, and endometrial cancers.

3.1. Ovary

Based on previous studies, high expression of HOTTIP has been significantly associated with poor survival rates, advanced stages, and lymph node metastasis in ovarian cancer patients compared to those with lower HOTTIP expression. Experimental knockdown of HOTTIP in OVCAR3 and A2780 cells resulted in a significant reduction in S phase cell numbers and cell invasion abilities as compared to control groups. Moreover, HOTTIP knockdown led to decreased protein levels of WNT1 and β -catenin in A2780 cells, suggesting the inhibition of the WNT signaling pathway in ovarian cancer cells [31]. Additionally, a recent study demonstrated a positive feedback loop between IL-6 and PD-L1 and between HOTTIP and IL-6 in ovarian cancer tissues. This feedback loop involving HOTTIP, IL-6, and PD-L1 promoted immune escape and immune evasion of ovarian cancer cells, ultimately inhibiting T-cell proliferation [43]. Another study revealed that HOTTIP depletion via shRNAs resulted in decreased phosphorylation levels of MEK and ERK, suppressed proliferation and invasion, and promoted apoptosis in ovarian cancer cells. Conversely, HOTTIP overexpression reversed these effects, suggesting that high expression of HOTTIP activates the MEK/ERK pathway, promoting proliferation, migration, and invasion of ovarian cancer cells [44]. Moreover, HOTTIP overexpression in ovarian cancer cells sequestered ASK1/JNK signaling, thereby inducing ovarian cancer progression while down-regulation of miR-148a-3p and overexpression of AKT2 counteracted the effects of HOTTIP reduction [45]. Notably, HOTTIP overexpression was significantly associated with cisplatin resistance in ovarian cancer cells, and HOTTIP was found to sponge miR-205, which directly targeted ZEB2 expression. Furthermore, HOTTIP knockout inhibited clonogenic potential, and

Table 1. The multifaceted involvement of HOTTIP in gynecologic malignancies.

Cancer Type	Suppression	Stimulation	Result	Refs.
Ovary	-	Increased the protein levels of WNT1 and β-catenin in A2780 cells.	High expression of HOTTIP was correlated with poor survival rate, advanced stage and lymph node metastasis	[31]
	T cell response against tumor cells	Increased expression of PD-L1 and IL-6 level.	Inhibition T-cell proliferation and ultimately accelerating the immune escape of OC cells	[43]
	-	Phosphorylation levels of MEK and ERK	Increased the proliferation and invasion and suppressed apoptosis of OC cells	[44]
	ASK1/JNK signaling, miR-148a-3p	AKT2, NLRP1 inflammasome-mediated pyroptosis	HOTTIP promoted ovarian cancer progression by regulating cell pyroptosis and proliferation.	[45]
	miR-205	ZEB2, clonogenic potential, NF-κB activation, and increased the expression of SOX2, OCT4, and NANOG	Over-expression of HOTTIP was remarkably associated with cisplatin resistance in A2780 and SK-OV-3 cells of OC	[46]
	The cell cycle arrest in G0/G1 phase, cell apoptosis rate	HIF-1α expression and VEGF concentration, colony formation, cell viability, proliferation, migration, and invasion	HOTTIP has positive correlation with HIF-1α to promote hypoxic ovarian cancer development and metastasis.	[47]
Breast	-	-	High expression of HOTTIP was correlated with worse survival outcome, shorter OS, clinical pathologic factors, tumor size, lymph node status, Her-2 status, and TNM stage	[50]
	-	Up-regulation of HOXA11	HOTTIP acts as a putative tumor progression in BC cells by HOXA11 up-regulation in MCF-7 cell line	[51]
	-	Up-regulation of cyclin D1 and PCNA, PI3K/AKT pathway	Higher expression of HOTTIP showed worse survival outcome, tumor size, expressions of ER, HER2, and PR and progression of BC in SKBR3 and MCF-7 cell lines	[52]
		-	High expression of HOTTIP was correlated with migration, invasion and EMT, increased N-cadherin, Snail and decreased E-cadherin level in MDA-MB-231 and MDA-MB-468 cell lines	[53]
	miR-148a-3p, CK14 and CK18	WNK1, expression of OCT4 and SOX2	HOTTIP could exert an oncogenic effect in BC development by promotion cell clonogenicity, and shorter overall survival	[54]
	-	-	There was a significant correlation between CC genotyping of rs1859168 SNP and down-regulation of miR-615-3p levels with progression of BC	[55]
Cervix	-	-	HOTTIP up-regulation was associated with increased tumor characteristics such as ability of proliferation, migration and invasion in HeLa and C-33A the cervical cancer cells	[56]
	-	-	There was a correlation between rs2067087 variant of HOTTIP and the risk of cervical cancer	[57]
Endometrium	-	-	HOTTIP expression was correlated with FIGO stages, histological grade, myometrial invasion depth, lymphatic vessel infiltration status, lymph node metastasis and survival rate	[29]

NF-κB activation, and decreased the expression of stem cell markers SOX2, OCT4, and NANOG, with the effect being reduced by miR-205 [46]. HOTTIP silencing was also associated with cell cycle arrest, apoptosis, suppressed colony formation, reduced cell proliferation, migration, and invasion, and negative regulation of HIF-1α expression and VEGF concentration in ovarian cancer cells. This suggested that HOTTIP forms a positive feedback loop with HIF-1α, promoting hypoxic ovarian cancer development and metastasis [47]. Combining immunopoint inhibitors with small molecule inhibitors has shown promising results in enhancing the anti-tumor activity of immune cells in ovarian cancer, potentially improving efficiency and reducing side effects [48]. Furthermore, high-risk ovarian cancer patients exhibited higher infiltration of macrophages and tumor-associated fibroblasts, leading to a significantly worse prognosis compared to low-risk

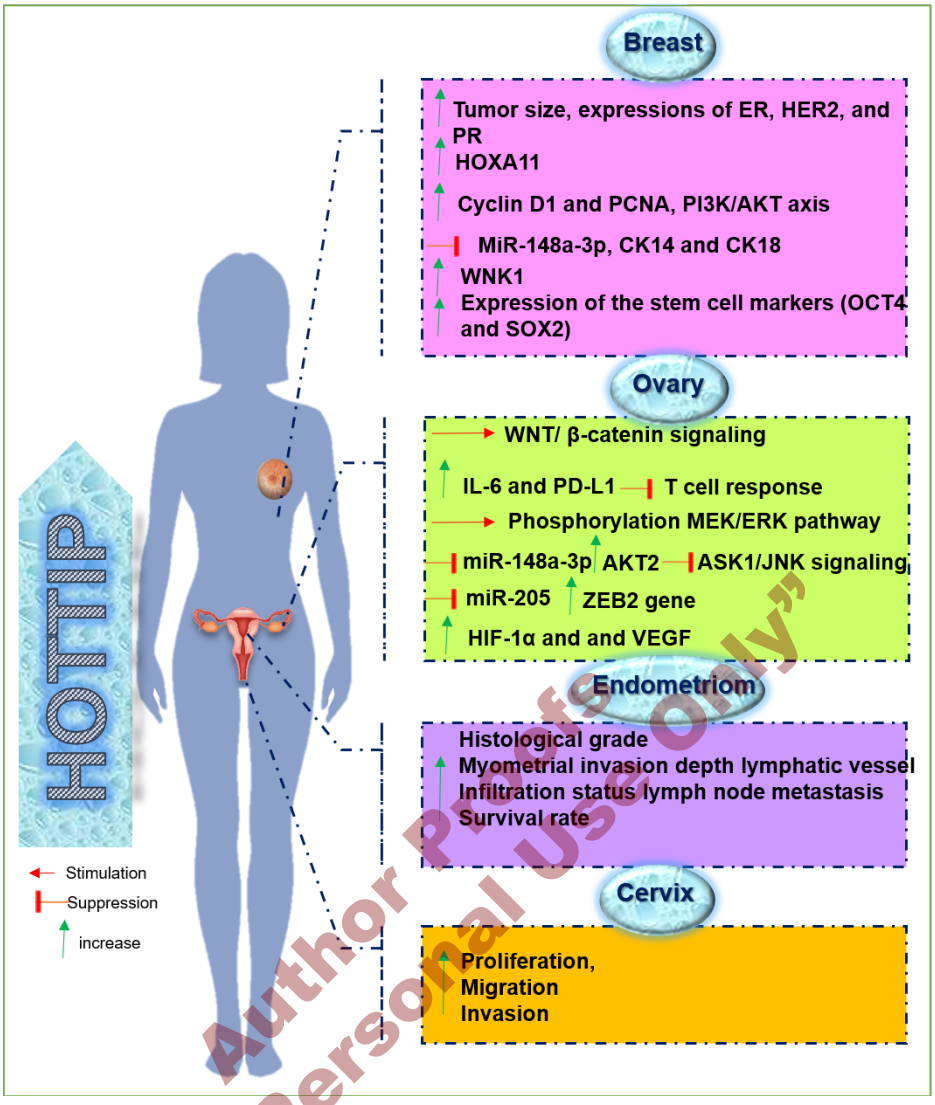

Fig. (1). Extensive research has aimed to clarify the connection between elevated levels of HOTTIP (HOXA transcript at the distal tip) and the dysregulated expression of various genes, as well as disrupted signaling pathways in gynecologic cancers. These studies have shown that increased HOTTIP expression is associated with the abnormal activation or suppression of genes that are vital for key cellular processes, including cell proliferation, apoptosis, invasion, metastasis, angiogenesis, and hormone signaling pathways.

patients. Additionally, a pyroptosis-related ceRNA regulatory network was constructed, revealing a competitive endogenous inhibition correlation between LINC01094, KRT7-AS, MYCNOS, ZNF32-AS2, AC012236.1, and pyroptosis-related genes such as IRF1, NOD1, GSDMC, NLRP1, PLCG1, GSDME, and GZMB. Notably, LINC01094 and KRT7-AS were found to be overexpressed in ovarian cancer cell lines [49]. Overall, these findings suggest that HOTTIP can serve as a prognostic biomarker and a potential therapeutic target in ovarian cancer.

3.2. Breast

A recent meta-analysis study has revealed a close association between high expression of the long noncoding RNA HOTTIP and unfavorable survival outcomes in BC. The study found that elevated HOTTIP expression was correlated with shorter overall survival, as well as clinical and pathological factors such as tumor size, lymph node status, Her-2 status, and TNM stage [50]. In vitro experiments using the MCF-7 cell line demonstrated that HOTTIP acts as a potential driver of tumor progression in BC by up-regulating HOXA11. Functional assays, including CCK-8 assays and examination in nude mice, showed that silencing HOTTIP suppressed cell proliferation, colony formation ability, and cell cycle progression, resulting in increased accumulation of MCF-7 cells in the G2/M-phase and decreased tumor growth [51]. Another study revealed that overexpression of HOTTIP was associated with altered cell cycle regulation, increased colony formation, and enhanced cell viability through up-regulation of cell cycle regulators such as cyclin D1 and PCNA. Kaplan-Meier analysis further demons-

trated that BC patients with higher HOTTIP expression had worse survival outcomes compared to those with lower expression. The expression level of HOTTIP was also found to correlate with tumor size, as well as the expression of estrogen receptor (ER), HER2, and progesterone receptor (PR) in BC [52]. Additionally, the HOTTIP/PI3K/AKT axis was implicated in BC progression and inhibition of cell apoptosis in SKBR3 and MCF-7 cell lines. Silencing HOTTIP was shown to suppress migration, invasion, and epithelial-mesenchymal transition (EMT) in MDA-MB-231 and MDA-MB-468 cell lines, as evidenced by reduced N-cadherin and Snail expression, and increased E-cadherin levels [53]. Han et al. revealed that up-regulation of HOTTIP promoted BC through sponging miR-148a-3p and increasing the expression of WNK1 in MCF7 and T47D cell lines. Functional assays demonstrated that HOTTIP exerted an oncogenic effect in BC development by enhancing cell clonogenicity and regulating the stemness of BC stem cells (BCSCs) through the up-regulation of OCT4 and SOX2, as well as the down-regulation of CK14 and CK18 as differentiation markers. Higher expression of HOTTIP was also associated with shorter overall survival [54]. Furthermore, a recent study revealed a significant correlation between the CC genotyping of rs1859168 and HOTTIP expression and miR-615-3p levels. Elevated expression of HOTTIP showed a negative correlation with miR-615-3p levels in the serum of BC patients. The CC genetic variants of the rs1859168 genotype exhibited significantly higher levels of HOTTIP and lower levels of miR-615-3p compared to the AA genotype [55]. Collectively, these findings suggest that the long noncoding RNA HOTTIP may serve as a prognostic biomarker and a promising therapeutic target for BC.

3.3. Cervix

Liu et al. investigated the impact of depleting HOTTIP using a HOTTIP-siRNA transfection strategy on tumor characteristics in cervical cancer cells, specifically HeLa and C-33A cells. The results demonstrated that depletion of HOTTIP significantly suppressed the ability of proliferation, migration, and invasion in these cells [56]. Additionally, a significant correlation was observed between the rs2067087 variant of HOTTIP and the level of cervical cancer. Furthermore, the H19 rs2839698 single nucleotide polymorphism (SNP) was found to be associated with the risk of developing cervical cancer [57]. These findings collectively suggest that HOTTIP may hold promise as a diagnostic and therapeutic target for the management of cervical cancer.

3.4. Endometrium

In a recent study, it was found that the expression level of HOTTIP is significantly higher in endometrial cancer tissues compared to adjacent tissues. Moreover, there was a statistically significant difference in the relative expression level of HOTTIP among different FIGO stages, histological grades, myometrial invasion depths, lymphatic vessel infiltration statuses, and lymph node metastasis in endometrial carcinoma tissues. Kaplan-Meier survival analysis revealed that the low-expression group had higher 5-year survival rates and longer survival times compared to the high-expression group [29]. These findings collectively suggest that HOTTIP plays a novel role in the treatment of endometrial cancer.

CONCLUSION

Growing evidence suggests that the HOTTIP plays crucial roles in the tumorigenesis and progression of BC and GCs by stimulating various cellular processes. These include key signaling pathways such as WNT/β-catenin, MEK/ERK, NF-κB, HIF-1α, HOXA11, and PI3K/AKT, while also suppressing the ASK1/JNK pathway. Mechanistically, HOTTIP influences the expression of several mRNAs, including PD-L1, IL-6, ZEB2, NF-κB, SOX2, OCT4, NANOG, VEGF, cyclin D1, PCNA, and WNK1.

Additionally, HOTTIP contributes to the pathogenesis of BC and GCs by sponging various miRNAs such as miR-148a-3p and miR-205. This interaction has been linked to poorer clinical outcomes, advanced disease stages, and distant metastases. In tumor samples from patients, elevated HOTTIP expression is positively associated with tumor size, lymphatic metastasis, and TNM stages.

HOTTIP significantly impacts tumor development processes like cell proliferation, invasion, migration, and apoptosis. Changes in HOTTIP expression with the upregulation of related proteins, enhance the developmental growth and regulate cell cycle transitions.

While this review highlights the potential effects of HOTTIP on various gynecologic tumors, the precise molecular mechanisms underlying its influence on GCs remain unclear. Therefore, further research is essential to fully understand its dysregulation and its potential as a biomarker for diagnosis, prognosis, and targeted therapy in these malignancies.

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The authors declare no conflict of interest financial or otherwise.

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