Role of long non-coding RNA HCG11 in human cancers: From molecular mechanisms to clinical applications (Review)

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Abstract. Long non-coding RNAs (lncRNAs) are transcripts >200 nucleotides in length that have no protein-coding potential and are important regulators of tumor development. Among them, HLA complex group 11 (HCG11) is a newly discovered lncRNA encoded by a gene located on chromosome 6p22.2, which consists of one exon. In recent years, interest in target molecules has increased because of their dysregulated expression in a number of cancers and their notable association with clinicopathological variables. Growing evidence has indicated that HCG11 is involved in tumor development mainly through interactions with target proteins, the sequestration of microRNAs and the participation of the MAPK, PI3K/AKT and Notch/hairy and enhancer of split-1 pathways. Together, the molecular mechanisms involved in the malignant tumor phenotype include proliferation, invasion, migration, apoptosis, cell cycle, drug resistance and epithelial-mesenchymal transition. The expression of HCG11 is closely related to tumor grade, differentiation, TNM stage, lymph node metastasis and prognosis. The present review provides an overview of the abnormal expression pattern, molecular mechanism and clinical relevance of HCG11 in malignant tumors. HCG11 has potential for use as a diagnostic biomarker and a therapeutic target for cancer treatment.

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Contents

1. Introduction

Due to its concealment, recurrence and difficulty in early diagnosis, cancer leads to poor survival outcomes and unfavorable prognosis in affected patients across the globe (1). The increase in worldwide cancer incidence and mortality rates places substantial strain on public health and socioeconomic resources. Globally, ~20 million new cancer cases and 9.7 million cancer-related mortalities occurred in 2022 (2). Cancer progression is complex and occurs because of various gene mutations, epigenetics and environmental factors (3,4). Although targeted therapy and immunotherapy have improved the treatment efficacy for tumors, numerous patients still have a poor prognosis because of the heterogeneity of tumors, individual differences and the inherent limitations of existing treatment methods (5,6). It is important to understand tumor occurrence and progression along with novel diagnostic and treatment interventions.

Long non-coding RNAs (lncRNAs) are transcription products >200 nucleotides that do not have the capacity to encode proteins (7). lncRNAs were first considered transcriptional noise with no function because of their non-coding potential and were not given notable attention. With the emergence of high-throughput sequencing technologies, lncRNAs have been demonstrated to function as transcriptional regulators, protein scaffolds or decoys, epigenetic modifiers, competitive endogenous RNA (ceRNA) sponges for microRNAs (miRNAs/miRs), or hosts for certain small peptides. They have biological functions in cell proliferation, migration, invasion, drug resistance and epithelial-mesenchymal transition (EMT) (8,9). Thus, they are emerging players in human malignant tumors. In addition, lncRNAs have strong efficiency, specificity and stability in

various tissues and have potential efficacy as biomarkers for cancer diagnosis, prognosis and treatment strategies.

HLA complex group 11 (HCG11) is an lncRNA first identified and reported in 2016, which is encoded by a gene located on chromosome 6p22. According to the NCBI-Gene database (https://www.ncbi.nlm.nih.gov/gene/493812), HCG11 (Gene ID: 493812) contains one transcript and one exon, covering 5,696 nucleotides in total (Fig. 1). Analysis using lncATLAS (http://lncatlas.crg.eu/) indicated that HCG11 is localized mainly in the cytoplasm (Fig. 2). Through the use of the online GEPIA2 tool (http://gepia.cancer-pku.cn/detail.php?gene=HCG11), notable alterations in the levels of HCG11 have been observed across various cancers, including adrenocortical carcinoma, bladder urothelial carcinoma, cervical squamous cell carcinoma and endocervical adenocarcinoma, ovarian serous cystadenocarcinoma, pancreatic adenocarcinoma, thymoma, uterine corpus endometrial carcinoma and uterine carcinosarcoma (Fig. 3). HCG11 exerts diverse biological roles in tumors, regulating the cell cycle, proliferation, migration, invasion, EMT and drug resistance, and its function varies across different cancer types. The present review summarizes recent advances in understanding the expression profiles, clinical relevance, molecular regulatory mechanisms and biological functions of HCG11 in cancer. It also discusses the potential of HCG11 as a therapeutic target and diagnostic biomarker, aiming to provide mechanistic insights and references to support future research and clinical translation.

2. Functional role of HCG11 in different cancers

Numerous studies have indicated a strong relationship between reduced levels of HCG11 and unfavorable outcomes in individuals with different types of cancer (Table I) (10-25). The functions and mechanisms of HCG11 in cancer development are summarized in Table II (10,11,13-38) and III (10,14,16,17,19,20,22,24,25,28,29,37,38). Collectively, Table II illustrates that HCG11 has both oncogenic and tumor-suppressive effects in a cancer-specific manner, influencing malignant characteristics through ceRNA interactions and established signaling pathways. Table III confirms these results in xenograft models, showing that manipulating HCG11 expression markedly impacts tumor growth *in vivo*.

Colorectal cancer (CRC). CRC is the third most common malignant tumor worldwide (39). While CRC and its complications may be addressed using surgical treatment and adjuvant therapy, one-fifth of patients with CRC already have metastasis at the time of diagnosis; thus, the prognosis of patients with CRC is negative and early diagnosis and timely intervention are important (40). Recent evidence suggests that CRC cells markedly upregulate HCG11 (26). A functional study has shown that the absence of HCG11 weakens CRC cell proliferation, migration and invasion and promotes apoptosis (41). Mechanistically, miR-26-5p is the downstream target of HCG11 and is negatively regulated by it. miR-26-5p can bind to cAMP-regulated phosphoprotein 19 (ARPP19), and the inhibition of miR-26-5p can counteract the effects of HCG11 on the growth and metastatic potential of CRC cells while also downregulating ARPP19 expression, confirming that HCG11 exerts its oncogenic role in CRC via the miR-26-5p/ARPP19 axis (26).

Radiotherapy and chemotherapy are the main treatment methods for CRC. Capecitabine is a chemotherapy drug used for various malignant tumors, including CRC, but it can enhance the tolerance and selectivity of tumor cells (41). However, without reliable monitoring markers, the emergence of chemoresistance cannot be identified in a timely manner during chemotherapy. Patients with CRC express higher levels of HCG11, and the expression of HCG11 decreases in patients receiving capecitabine treatment. Further *in vitro* experiments have revealed that capecitabine can downregulate the expression of HCG11 in CRC cells to induce tumor cell apoptosis, indicating that HCG11 is a poor biomarker in patients with CRC (42). 5-Fluorouracil (5-FU) is a first-line anticancer drug traditionally used for patients with CRC, but resistance is the main obstacle limiting its clinical application. Therefore, understanding the exact mechanism of 5-FU resistance is crucial for developing treatment strategies for patients with CRC. HCG11 is markedly upregulated in CRC tissues and cell lines and is positively associated with 5-FU resistance in patients with CRC. Similarly, compared with that in parental CRC cells, the expression of HCG11 is markedly upregulated in 5-FU-resistant CRC cells. Further investigation revealed that the mechanism involves HCG11 acting as a ceRNA to absorb miR-144-3p, resulting in the de-repression of pyruvate dehydrogenase kinase 4 (PDK4) as a target of miR-144-3p in CRC; this regulatory axis ultimately reprograms cellular glucose metabolism and enhances 5-FU resistance of CRC cells (27).

Pancreatic carcinoma (PC). PC is considered one of the most malignant cancers worldwide and ranks as the fourth leading cause of cancer-related mortality. The 5-year survival rate for patients with PC is only 13%, which is much lower than that for patients with other cancers (43). Currently, surgical resection, chemotherapy and molecular targeted therapy can effectively improve the prognosis of early-stage PC, but these treatments are ineffective for advanced PC, especially for those with systemic metastasis. This highlights the need to identify the molecular drivers of PC to develop more effective treatments targeting these factors. Through analysis of the GEO database and the lncRNA disease database, it was found that HCG11 is markedly upregulated in patients with PC, especially in male patients (44). Jing *et al* (45) also reported that HCG11 is notably upregulated in PC tissues through analysis of the GEPIA database. It competitively binds to miR-26b-5p and releases its inhibition of the target gene collagen type XII alpha 1 chain, driving the progression of PC. Bioinformatics analysis revealed that HCG11 upregulates the expression of murine double minute 2 (MDM2) through competitive targeting of miR-579-3p. In mouse models lacking HCG11 expression, the expression of HCG11 and MDM2 decreased, whereas the expression of miR-579-3p increased, and the tumor volume and weight markedly decreased. These findings demonstrate the oncogenic role of the HCG11/miR-579-3p/MDM2 axis in PC (28).

Hepatocellular carcinoma (HCC). HCC is the most common primary liver malignancy worldwide. Owing to its high recurrence rate and the lack of effective therapeutic drugs, the 5-year survival rate is ~10% (46). The enrichment level of

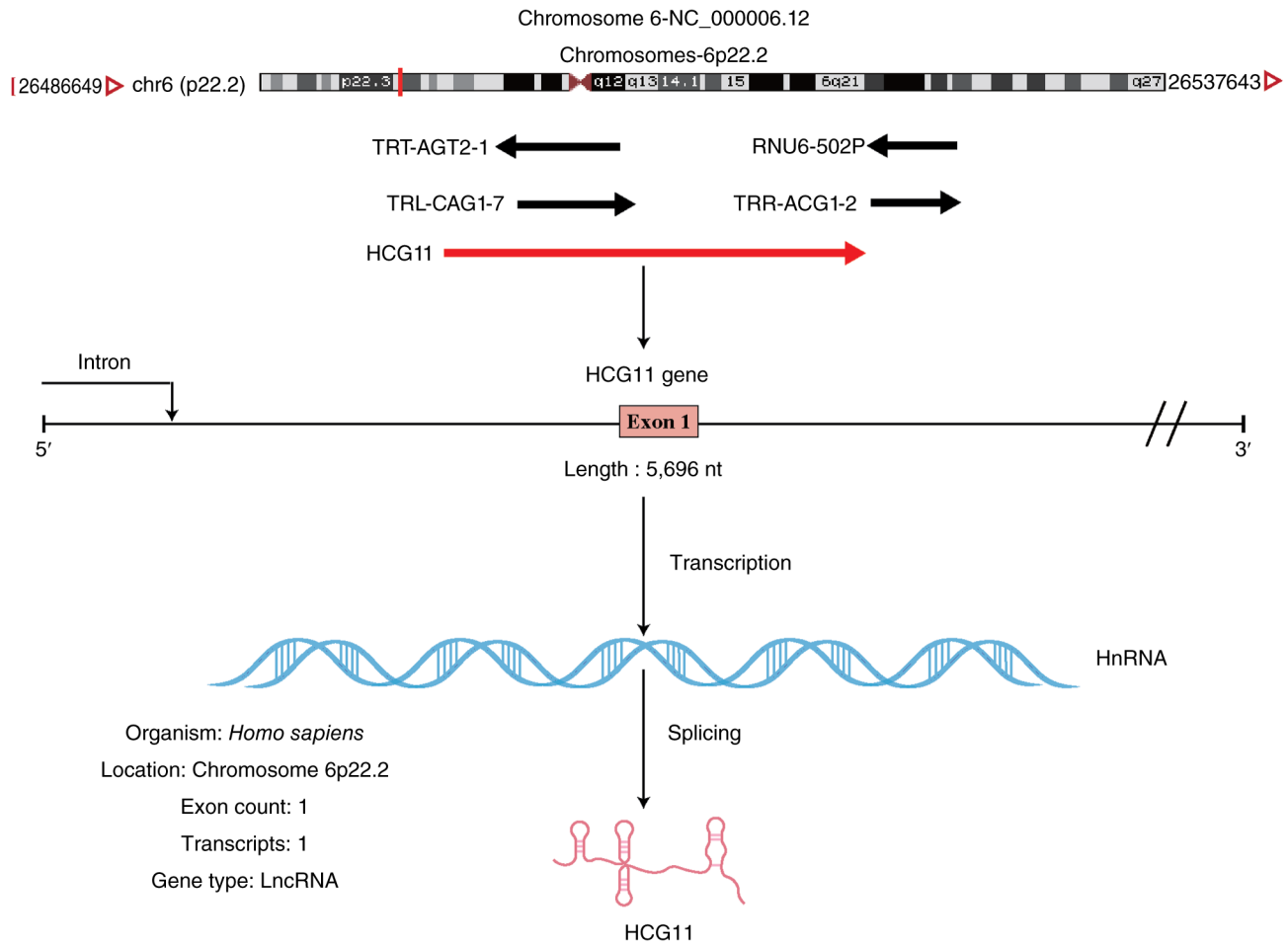

Figure 1. Schematic of lncRNA HCG11. HCG11 is located on human chromosome 6p22.2 and contains only one transcript and one exon (extracted from the NCBI-Gene database). lncRNA, long non-coding RNA; HCG11, HLA complex group 11; hnRNA, heterogeneous nuclear RNA.

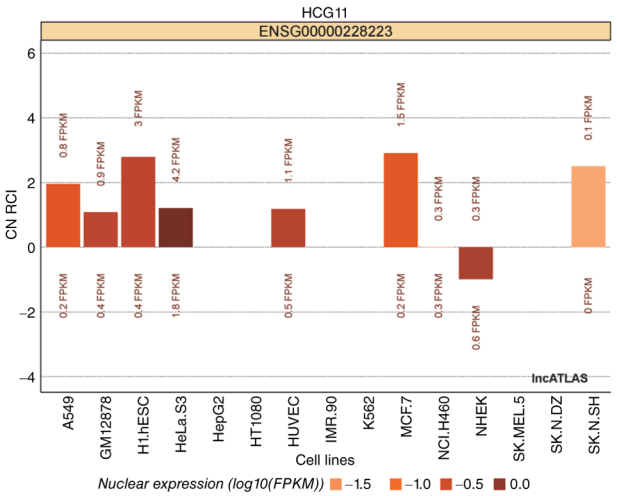

Figure 2. HCG11 is predominantly localized in the cytoplasm of common cell lines. Bar plot from lncATLAS analysis (http://lncatlas.crg.eu/). HCG11, HLA complex group 11; FPKM, fragments per kilobase million; CN RCI, cellular normalized read count index.

HCG11 is markedly increased in HCC cell lines. Conversely, silencing HCG11 expression can notably inhibit the proliferation, migration and autophagy of HCC cells (10). The expression levels of HCG11 in HCC tissues are greater than that in corresponding normal tissues, and analysis of survival curves demonstrated that patients in the high-expression group of HCG11 had a markedly lower 5-year survival rate compared with those in the low-expression group (10). Mechanistic studies have shown that HCG11 promotes the expression of autophagy-related 12 (ATG12) by sponging miR-26a-5p, thus facilitating the progression of HCC (10). Mitogen-activated protein kinase (MAPK) serves a complex role in cancer development, but MAPK has been confirmed to control cell differentiation, proliferation, and the survival and migration of specific cancer cells (47). Xu *et al* (11) reported that the mRNA and protein levels of HCG11 and insulin-like growth factor 2 mRNA-binding protein 1 (IGF2BP1) in 20 patients with HCC were markedly greater in tumor tissues than in adjacent tissues. Knockdown of both HCG11 and IGF2BP1 inhibited the activity of MAPK pathway proteins and induced apoptosis in HCC cells through the mitochondrial pathway. In conclusion, HCG11 has potential to become a biomarker for the diagnosis and personalized treatment of patients with HCC, providing more accurate prognostic assessment and treatment strategies.

Prostate cancer (PCa). PCa remains a significant health challenge with >375,000 deaths annually among men worldwide,

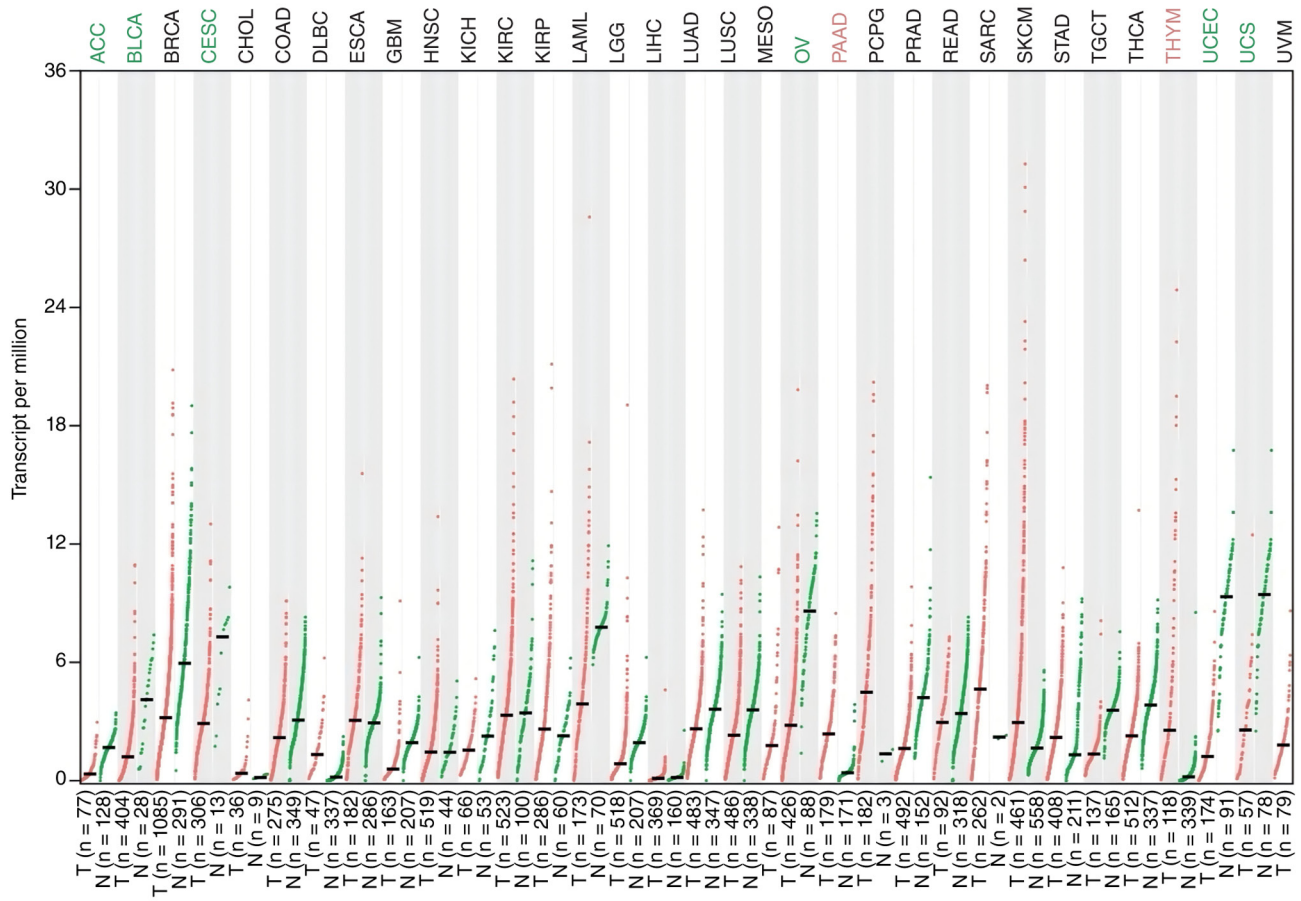

Figure 3. HCG11 expression patterns in different cancer and normal tissues were analyzed using the GEPIA2 online database. HCG11, HLA complex group 11; T, tumor; N, normal.

and it often progresses slowly and lacks early characteristic symptoms (48). Although early detection and treatment are effective, advanced tumors often metastasize to the bones, making treatment more challenging. A study has indicated that lncRNAs are potential therapeutic targets for PCa (49). Analysis of two publicly available gene expression databases, GSE55945 and GSE45016, revealed that the expression of HCG11 was lower in PCa tissues than in non-tumor tissues in both databases. Further analysis revealed decreased HCG11 expression in 21 PCa tissues compared with 6 normal prostate tissues from separate donors. A lower HCG11 level was associated with a poorer survival rate among patients with PCa (12). Overexpression of HCG11 inhibited proliferation, metastasis and invasion and induced apoptosis in PCa cell lines (29). Further research has shown that overexpression of HCG11 inhibits the growth of PCa cells by downregulating miR-543 expression, thus inhibiting the phosphatidylinositol 3-kinase/protein kinase B (PI3K/AKT) signaling pathway, providing a new target for the treatment of PCa (29).

Glioma. Glioma is the most common primary central nervous system tumor, affecting millions of people worldwide. Owing to its high metastasis rate and drug resistance rate, it has considered among the most aggressive and lethal cancers (50). Moreover, because the tumor is difficult to completely remove, comprehensive treatment is advocated to delay recurrence and prolong survival. However, most treatments are ineffective and often lead to recurrence and mortality (51). An insufficient understanding of the mechanism of glioma is the main reason for the poor treatment effect. Therefore, exploring and clarifying the mechanism of glioma occurrence and development is important.

Multiple studies have shown that HCG11 serves an important role in the pathogenesis of glioma. Previous research indicates that, through clinical data analysis, the expression level of HCG11 in glioma is lower than that in normal glioma cells (13-15,52). Kaplan-Meier analysis revealed that patients with high levels of HCG11 have a greater overall survival (OS) rate than those with low levels of HCG11. These data suggest that HCG11 is important for the prognosis of glioma (13,14). Ma *et al* (15) constructed a HCG11/miR-590-3p/cell adhesion molecule 2 (CADM2) regulatory network, revealing that HCG11 upregulates CADM2 expression through miR-590-3p, thus inhibiting the proliferation and migration of glioma cells.

Clinical studies have shown that the possible molecular mechanisms of glioma resistance include mutations in gene targets under the action of chemotherapy drugs and a reduction in tumor cell apoptosis (14,52). In glioma, downregulation of HCG11 exerts dual and seemingly contradictory effects, as it inhibits cell proliferation and promotes apoptosis, which would be considered antitumor effects, but it also reduces the sensitivity of glioma cells to the chemotherapeutic agents imatinib and temozolomide. This suggests that while targeting HCG11 alone may suppress glioma progression, it could

Table I. Clinical value of HCG11 in various cancers.

First author, year	Cancer type	No. of clinical samples	Expression change	Clinical characteristics	Prognostic implication of HCG11 upregulation	Role	(Refs.)
Li *et al*, 2019	Hepatocellular carcinoma	65	Upregulation	TNM stage and 5-year survival rate	Poor	Oncogene	(10)
Xu *et al*, 2017	Hepatocellular carcinoma	20	Upregulation	Progression of the tumor	Poor	Oncogene	(11)
Zhang *et al*, 2016	Prostate cancer	21	Downregulation	Age, LN status, preoperative PSA level, Gleason score and 5-year biochemical recurrence rate	Good	Tumor suppressor gene	(12)
Zhang *et al*, 2019	Glioma	84	Downregulation	Overall survival	Good	Tumor suppressor gene	(13)
Chen *et al*, 2019	Glioma	88	Downregulation	Overall survival	Good	Tumor suppressor gene	(14)
Ma *et al*, 2022	Glioma	42	Downregulation	TNM stage	Good	Tumor suppressor gene	(15)
Zhang *et al*, 2019	Gastric cancer	47	Upregulation	TNM stage	Poor	Oncogene	(16)
Xie *et al*, 2023	HR-positive breast cancer	30	Downregulation	Tumor size	Good	Tumor suppressor gene	(17)
Fan *et al*, 2020	Non-small cell lung cancer	62	Down-regulation	Tumor size, TNM stage and lymph nodes metastasis	Good	Tumor suppressor gene	(18)
Wang *et al*, 2020	Non-small cell lung cancer	20	Down-regulation	-	Good	Tumor suppressor gene	(19)
Mao *et al*, 2021	Non-small cell lung cancer	50	Down-regulation	Tumor size	Good	Tumor suppressor gene	(20)
Wang *et al*, 2020	Osteosarcoma	20	Upregulation	GTM stage and tumor size	Poor	Oncogene	(21)
Gu *et al*, 2021	Osteosarcoma	50	Downregulation	Tumor size and overall survival	Good	Tumor suppressor gene	(22)
Xue *et al*, 2020	Laryngeal carcinoma	30	Downregulation	-	Good	Tumor suppressor gene	(23)
Zheng *et al*, 2022	Nasopharyngeal Carcinoma	126	Upregulation	Tumor stage, lymphatic metastasis and poor prognosis	Poor	Oncogene	(24)
Zhang *et al*, 2025	Multiple myeloma	55	Upregulation	Overall survival and abnormal cytogenetics	Poor	Oncogene	(25)

HR, hormone receptor; HCG11, HLA complex group 11; LN, lymph node; GTM, Grade, Tumor, Metastasis (Enneking staging system); PSA, prostate-specific antigen.

Table II. Biological role of HCG11 in diverse tumors.

First author, year	Cancer type	Cell lines	Expression	Effect *in vitro*	Regulatory mechanism	Role	(Refs.)
Li *et al*, 2019	Hepatocellular carcinoma	MHCC97-H, Hep3B	Upregulation	Proliferation ↑, metastasis ↑, autophagy ↑, apoptosis ↓	HCG11/miR-26a-5p/ ATG12	Oncogene	(10)
Xu *et al*, 2017	Hepatocellular carcinoma	Huh7, HepG2, SMMC-7721, SK-HEP-1	Upregulation	Proliferation ↑ and invasion ↑	MAPK signaling pathway	Oncogene	(11)
Zhang *et al*, 2019	Glioma	A172, U251, U87MG, U118	Downregulation	Proliferation ↓, apoptosis ↑	HCG11/miR-4425/MTA3	Tumor suppressor gene	(13)
Chen *et al*, 2019	Glioma	U87 and U251	Downregulation	Proliferation ↓, cell cycle arrest ↑, apoptosis ↑	HCG11/miR-496/CPEB3	Tumor suppressor gene	(14)
Ma *et al*, 2022	Glioma	U251, U87, U-118MG, SHG-44	Downregulation	Proliferation ↓, migration ↓	HCG11/miR-590-3p/ CADM2	Tumor suppressor gene	(15)
Zhang *et al*, 2019	Gastric cancer	AGS, BGC-823, SGC-7901, SWMGC-803480	Upregulation	Proliferation ↑ and migration ↑	PI3K/AKT signaling pathway	Oncogene	(16)
Xie *et al*, 2023	HR-positive breast cancer	MCF7 and BT474	Downregulation	Proliferation ↓	HCG11/SRSF1/β-catenin	Tumor suppressor gene	(17)
Fan *et al*, 2020	Non-small cell lung cancer	NCI-H23	Downregulation	Viability ↓, migration ↓ and invasion ↓	HCG11/miR-522-3p/ SOCS5	Tumor suppressor gene	(18)
Wang *et al*, 2020	Non-small cell lung cancer	A549, SPC-A1, H1299, H1650, H1975, PC-9	Downregulation	Proliferation ↓, apoptosis ↑	HCG11/miR-224-3p/ caspase-3	Tumor suppressor gene	(19)
Mao *et al*, 2021	Non-small cell lung cancer	A549, PC9, NCIeH1975, NCIeH522	Downregulation	Proliferation ↓	HCG11/IGF2BP2/LATS1	Tumor suppressor gene	(20)
Wang *et al*, 2020	Osteosarcoma	MG63 and U2OS	Upregulation	Proliferation ↑	HCG11/miR-579/MMP13	Oncogene	(21)
Gu *et al*, 2021	Osteosarcoma	MG63, U2OS, HOS, 143B, Saos-2	Downregulation	Proliferation ↓, cell cycle ↓, DNA replication ↓	HCG11/miR-942-5p/ p27 Kip1	Tumor suppressor gene	(22)
Xue *et al*, 2020	Laryngeal carcinoma	SNU46, SNU899, AMC-HN-8	Downregulation	Proliferation ↓, apoptosis ↑	HCG11/miR-4469/ APOM	Tumor suppressor gene	(23)
Zheng *et al*, 2022	Nasopharyngeal Carcinoma	5-8F, CNE-1, CNE-2	Upregulation	Proliferation ↑, migration ↑, apoptosis ↓	HCG11/miR-490-3p/ MAP3K9	Oncogene	(24)
Zhang *et al*, 2025	Multiple myeloma	ARD, ARP1, AMO.1	Upregulation	Proliferation ↑, sensitivity to selinexor ↓	XPO1	Oncogene	(25)
Guo *et al*, 2023	Colorectal cancer	LOVO, HT-29, HCT15	Upregulation	Proliferation ↑, migration ↑, invasion ↑, apoptosis ↓	HCG11/miR-26b-5p/ ARPP19	Oncogene	(26)
Cui *et al*, 2022	Colorectal cancer	DLD-1, LoVo, Caco2, HT-29, HT-116, SW480,	Upregulation	Proliferation ↑, migration ↑, invasion ↑ and glucose metabolism ↑	HCG11/miR-144-3p/ PDK4	Oncogene	(27)

Table II. Continued.

First author, year	Cancer type	Cell lines	Expression	Effect *in vitro*	Regulatory mechanism	Role	(Refs.)
Xu *et al*, 2021	Pancreatic carcinoma	BxPC-3, SW1990, PANC-1, AsPC-1, Capan-2	Upregulation	Proliferation ↑, apoptosis↓	Notch/Hes1 signaling pathway	Oncogene	(28)
Wang *et al*, 2019	Prostate cancer	LNCaP, PC-3, C4-2B, HEK293T	Downregulation	Proliferation ↓, migration ↓, invasion ↓, apoptosis ↑	PI3K/AKT signaling pathway	Tumor suppressor gene	(29)
Zhang *et al*, 2021	Gastric cancer	AGS and HGC-27	Downregulation	Proliferation ↓, migration ↓ and invasion ↓	HCG11/miR-942-5p/ BRMS1	Tumor suppressor gene	(30)
Li *et al*, 2020	Ovarian cancer	TOV112D, A2780, SKOV3, ISOE80	Upregulation	Proliferation ↑, migration ↑ and invasion ↑	HCG11/miR-144-3p/ PBX3	Oncogene	(31)
Chen *et al*, 2022	Ovarian cancer	A2780 and SKOV3	Downregulation	Proliferation ↓, migration ↓ and EMT ↓	AKT signaling pathway	Tumor suppressor gene	(32)
Xu *et al*, 2024	Non-small cell lung cancer	A450-GEM	Downregulation	Drug resistance, proliferation, apoptosis and cell cycle	HCG11/miR-17-5p/p21	Oncogene	(33)
Yan *et al*, 2022	Osteosarcoma	SW1353, HOS, Saos-2, SOSP-9607, hFOB1.19	Upregulation	Proliferation ↑, migration ↑, invasion ↑, apoptosis ↓	HCG11/miR-1245b/ PKP2	Oncogene	(34)
Yan and Wang, 2023	Salivary adenoid cystic carcinoma	ACC-2, SACC-83, SACCLM	Downregulation	Proliferation ↓, migration ↓, and invasion ↓	HCG11/miR-1297/ EphA2	Tumor suppressor gene	(35)
Long *et al*, 2021	Vestibular schwannoma	VSs and HEI-193	Downregulation	Proliferation ↓, apoptosis ↑	HCG11/miR-620/ELK4	Tumor suppressor gene	(36)
Wu *et al*, 2021	Oral squamous cell carcinoma	TSCCA, CAL-27, FaDu	Downregulation	Proliferation ↓	HCG11/miR-455-5p/ PTPRS	Tumor suppressor gene	(37)
Liu *et al*, 2025	Thyroid cancer	TPC-1, KTC-1, WRO, B-CPAP, SW579, FTC-133	Downregulation	Proliferation ↓, migration ↓ and invasion ↓	STAT3/HCG11/ miR-450b-5p/TAS2R14	Tumor suppressor gene	(38)

↑, promoting; ↓, inhibiting; HCG11, HLA complex group 11; miR/miRNA, microRNA; HR, hormone receptor.

Table III. Effects of HCG11 on growth and metastasis of cancer xenografts.

First author, year	Cancer type	Animal models	Function	(Refs.)
Li *et al*, 2019	Hepatocellular carcinoma	Nude mice	↓↓ HCG11: ↓ tumor growth and weight	(10)
Chen *et al*, 2019	Glioma	6-week-old male BALB/C nude mice	↑↑ HCG11: ↓ tumor volume and weight	(14)
Zhang *et al*, 2019	Gastric cancer	Nude mice	↓↓ HCG11: ↑ tumor growth and weight	(16)
Xie *et al*, 2023	HR-positive breast cancer	5-week-old Balb/c nude mice	↑↑ HCG11: ↓ tumor volume and weight	(17)
Wang *et al*, 2020	Non-small cell lung cancer	Male athymic BALB/c nude mice	↑↑ HCG11: ↓ tumor volume and weight	(19)
Mao *et al*, 2021	Non-small cell lung cancer	4-week-old male BALB/c nude mice	↑↑ HCG-11: ↓ tumor growth	(20)
Gu *et al*, 2021	Osteosarcoma	5-week-old male BALB/c nude mice	↑↑ HCG-11: ↓ tumor growth	(22)
Zheng *et al*, 2022	Nasopharyngeal carcinoma	7-week-old female BALB/c nude mice	↓↓ HCG11: ↓ tumor growth and weight	(24)
Zhang *et al*, 2025	Multiple myeloma	8-week-old female severe immunodeficient NOD-Prkdcscid IL2rgtm1/ Bcgen mice	↓↓ HCG11: ↑ sensitivity to selinexor	(25)
Xu *et al*, 2021	Pancreatic carcinoma	Male nude mice	↓↓ HCG11: ↓ tumor growth	(28)
Wang *et al*, 2019	Prostate cancer	4-5-week-old female BALB/c nude mice	↑↑ HCG-11: ↓ tumor weight	(29)
Wu *et al*, 2021	Oral squamous cell carcinoma	Nude mice	↓↓ HCG11: ↑ tumor growth and weight, ↑ Ki67 expression	(37)
Liu *et al*, 2025	Thyroid cancer	4-6 week female BALB/c mice	↑↑ HCG11: ↓ tumor volume and weight	(38)

↑↑, HCG11 overexpression; ↑, promoting; ↓↓, HCG11 knockdown or knockout; ↓, inhibiting; HCG11, HLA complex group 11; HR, hormone receptor.

simultaneously promote chemotherapy resistance, indicating that HCG11 may serve as a context-dependent regulatory target for overcoming drug resistance in glioma (52).

Gastric cancer (GC). GC is a widespread malignant tumor worldwide, ranking fifth in terms of incidence and third in terms of mortality (53). Increasing evidence has revealed the importance of lncRNA as a key regulator in GC (54). A recent study has shown that HCG11 is highly expressed in GC tissue samples. Moreover, compared with early-stage GC (I + II), advanced-stage (III + IV) GC is markedly enriched in HCG11, indicating its crucial role in the development and progression of GC (16). Additionally, HCG11 is highly expressed in GC, and its knockdown inhibits proliferation and migration but accelerates apoptosis in GC cells. The subcellular localization of HCG11 has been studied using nuclear-cytoplasmic separation technology, and the results revealed that HCG11 aggregated mainly in the cytoplasm. RNA pull-down and luciferase reporter gene experiments demonstrated that HCG11 could regulate the expression of b-catenin (CTNNB1) and the Wnt signaling pathway to promote the proliferation and migration of GC cells. These findings suggest that HCG11 can act as a cancer gene in the progression of GC and may be a promising target for GC treatment (16).

Notably, another study reached the opposite conclusion. Compared with that in the normal human gastric epithelium cell line GES-1, the expression of HCG11 was downregulated in the GC cell lines AGS and HGC-27. The overexpression of HCG11 inhibited cell proliferation, migration and invasion in GC (30). Starbase predicted that HCG11 has binding sites for miR-942-5p, and TargetScan predicted that miR-942-5p has binding sites on the 3'-UTR of breast carcinoma metastasis suppressor gene 1 (BRMS1). Rescue experiments demonstrated that HCG11, as a ceRNA, mediated the ability of miR-942-5p to regulate the expression of BRMS1 and inhibited the proliferation, migration and invasion of GC cells (30). These different observations indicate that HCG11 plays complex and context-dependent roles in GC, exhibiting

both oncogenic and tumor-suppressive functions. This may be due to various factors, such as different clinical sample sources, isoform diversity and molecular interaction networks. Therefore, a deeper understanding of the molecular structure of HCG11 and its molecular mechanism in GC is needed.

Different studies have reported conflicting oncogenic and tumor suppressor roles of HCG11 in GC, which is largely attributed to the heterogeneity of cancer subtypes, different sources of clinical samples and different molecular regulatory networks. One study has shown that HCG11 is highly expressed in GC and promotes cell proliferation and migration through the miR-1276/CTNNB1/Wnt signaling pathway (16), whereas another study has reported that HCG11 inhibits tumor progression through the miR-942-5p/BRMS1 axis (30). This discrepancy is partly due to differences in the histological differentiation of GC specimens, clinical stage and source of surgical specimens. In addition, different detection methods, including cell line models and quantitative analysis platforms, have been used in different studies, resulting in inconsistent baseline expression levels of HCG11. Taken together, these findings suggest that the variable downstream miRNAs and target genes involved in the activity of HCG11 in different cellular environments constitute its dual function in GC.

Breast cancer (BRCA). BRCA is the leading cause of cancer-related mortality among women worldwide, causing 685,000 deaths in 2020, and this number continues to rise (55). Early detection and treatment are crucial for reducing the mortality rate of patients with BRCA. Mammography is currently the main technique for BRCA detection; however, its efficacy is limited. Therefore, identifying innovative molecular targets and indicators is crucial for enhancing diagnostic and therapeutic strategies. Recent studies have shown that HCG11, an important lncRNA, is highly important for the occurrence, progression and prognosis of BRCA (56,57). Analysis of 1,100 The Cancer Genome Atlas (TCGA)-BRCA datasets revealed that the expression of HCG11 was markedly upregulated in ER-negative and triple-negative breast cancer (TNBC) and that its upregulation was notably associated with OS (57). These findings were confirmed by reverse transcription-quantitative polymerase chain reaction (RT-qPCR), and similar results were observed in Brazilian patients with BRCA (56).

A recent study including 80 patients with BRCA demonstrated that ~73.3% of tumors with upregulated HCG11 expression were ER-negative, and this difference reached statistical significance (P=0.04) (58). Similarly, HCG11 was highly expressed in TNBC tissues. Specificity protein 1 (SP1) is a key factor in the progression of TNBC, and its stable expression promotes cell survival and invasion (59). HCG11, as a carcinogenic lncRNA, drives the progression of TNBC by stabilizing the SP1 protein, whereas EF24 exerts antitumor effects by targeting and inhibiting the HCG11/SP1 axis (60). In hormone receptor (HR)-positive tissues and cell lines, HCG11 expression is notably downregulated, and low expression is associated with tumor size (17). Knockdown of HCG11 promotes cell growth and colony formation. Mechanistically, HCG11 directly binds to the ribonucleotide reductase M (RRM) 1 and RRM2 domains of serine/arginine-rich splicing factor 1 (SRSF1), competitively blocking the interaction between SRSF1 and β-catenin and thus inhibiting the translation of β-catenin protein, leading to the downregulation of the downstream targets cyclin D1 and c-Myc of the Wnt signaling pathway and the inhibition of BRCA progression (17). These observations reinforce the heterogeneity of BRCA disease and, therefore, it is necessary to distinguish each subtype to more accurately assess the role of HCG11 in BRCA.

HCG11 is upregulated in TNBC and serves an oncogenic role by stabilizing the SP1 protein, whereas it is downregulated in HR-positive BRCA and acts as a tumor suppressor through the SRSF1/β-catenin signaling cascade. In addition to subtype heterogeneity, differences in the ethnicity of patient cohorts, tissue sampling criteria and testing strategies have contributed to these inconsistent results. These findings suggest that HCG11 serves a subtype-specific rather than a uniform role in BRCA, highlighting the importance of stratification according to molecular type (17,56).

Ovarian cancer (OC). OC is among the most lethal malignant tumors of the female reproductive system. Owing to the lack of specific symptoms, appropriate screening methods and effective treatment options, it is characterized by late diagnosis, chemotherapy resistance and a high recurrence rate (61). Therefore, determining the molecular mechanism of OC is urgently needed. A study reported by Li *et al* (31) revealed the biological role and molecular mechanism of HCG11 in OC and revealed that HCG11 was highly expressed in OC, the expression of miR-144-3p was downregulated, and the knockdown of HCG11 inhibited the growth of OC cells. An inhibitor of miR-144-3p could relieve the inhibitory effect of HCG11 on the growth of OC cells, and pre-B-cell leukemia homeobox 3 (PBX3) was the target gene of miR-144-3p. HCG11 prevented the cellular progression of OC by sponging miR-144-3p and downregulating PBX3. These results highlight the therapeutic target of HCG11 in OC (31). Notably, another study revealed low HCG11 expression in OC tissues using TCGA data and confirmed that HCG11 expression was lower in OC cells than in normal cells by RT-qPCR. Moreover, functional analysis revealed that HCG11 regulated the PI3K/AKT/mTOR pathway by targeting miR-1270/PTEN to inhibit OC cell proliferation, migration and EMT (32). The different conclusions of these two studies may come from the differences in clinical samples and cell lines. The molecular subtyping of cell lines or clinical samples in different studies may differ, leading to differences in gene expression, which highlights the complexity of the molecular mechanism of tumors. In future studies, clinical samples should be included and used to analyze the expression pattern and molecular mechanism of HCG11 in different tissue types.

Non-small cell lung cancer (NSCLC). There are two main types of lung cancer: Small cell lung cancer and NSCLC. Among them, NSCLC is of particular concern, as it accounts for ~85% of all lung cancer cases (62). In patients with NSCLC, low expression levels of HCG11 are associated with tumor size, TNM stage and lymph node metastasis. Functionally, HCG11 can inhibit the expression of cytokine signaling 5 in NSCLC by downregulating the expression of miR-522-3p, thus inhibiting the survival, migration and invasion of NSCLC (18). In addition, *in vivo* experiments demonstrated that the tumor volume and tumor size of HCG11-overexpressing mice were markedly lower than those of control mice (19).

As one of the most common subtypes of NSCLC, lung adenocarcinoma (LUAD) has high molecular and pathological heterogeneity (63). HCG11 expression is markedly downregulated in LUAD according to the UALCAN database, and this conclusion was subsequently confirmed by examining the expression of HCG11 in LUAD tissues and cells. Furthermore, it has been shown that HCG11 serves a tumor suppressor role in LUAD through the recruitment of insulin-like growth factor 2 binding protein 2 (IGF2BP2) to regulate large tumor suppressor 1 (LATS1) expression (20). Gemcitabine (GEM)-based combination chemotherapy can widely improve the survival rate of patients with advanced NSCLC, but resistance to GEM has become a key obstacle in the treatment of NSCLC. The development of new targets to enhance chemotherapy sensitivity is important for improving the clinical outcomes of patients with NSCLC. The expression of HCG11 in the GEM-resistant cell line A549 was markedly lower than that in A549. Bioinformatics prediction combined with multiple molecular biological experiments and dual luciferase assays confirmed that HCG11 could target and negatively regulate miR-17-5p, while p21 expression could be regulated by miR-17-5p. Rescue experiments revealed that HCG11 affected the sensitivity of A549-GEM cells to GEM through the miR-17-5p/p21 axis, which may provide a potential therapeutic strategy for NSCLC chemotherapy resistance (33).

Osteosarcoma. Osteosarcoma is the major primary malignant tumor of bone and is characterized by notable local invasiveness and propensity for metastasis. HCG11 serves a complex and important role in osteosarcoma. Wang *et al* (21) reported that HCG11 expression was upregulated in osteosarcoma and that HCG11 expression was associated with the TNM stage and tumor size of patients, indicating that it is a potential prognostic biomarker. In addition, HCG11 promoted osteosarcoma deterioration by sponging miR-579 and promoting matrix metallopeptidase 13 (MMP13) expression. This carcinogenic nature is further supported by the study of Yan *et al* (34), which revealed that HCG11 promoted the proliferation, migration and invasion of osteosarcoma cells and inhibited apoptosis by inhibiting the expression of miR-1245b-5p and subsequently epithelialized plakophilin-2 (PKP2). By contrast, another study proposed an opposite role for HCG11 in osteosarcoma. The study revealed that low HCG11 levels were strongly associated with increased tumor volume and shorter OS in patients with osteosarcoma. Moreover, HCG11 negatively regulates cell proliferation, the cell cycle, DNA replication and tumor growth *in vivo* by binding to miR-942-5p and IGF2BP2 to upregulate the expression of p27 Kip1 (22). These diverse findings collectively highlight the multifaceted and complex role of HCG11 in osteosarcoma. Its functions as an oncogene and tumor suppressor depend on its interactions with specific miRNAs and their cellular effects and are related to differences in clinical stage, genetic background and tissue origin of osteosarcoma samples, as well as different detection systems and experimental conditions.

Other malignant tumors. In addition to its expression in the aforementioned tumors, HCG11 is aberrantly expressed in a variety of tumors, such as multiple myeloma (MM), thyroid cancer (TC), oral squamous cell carcinoma (OSCC), vestibular schwannoma (VS) and endometrial carcinoma (EC). Salivary adenoid cystic carcinoma (SACC) is a rare salivary gland adenocarcinoma characterized by aggressive vascular and neural invasion, frequent metastasis and a high postoperative recurrence rate (64). Ephrin receptor A2 (EphA2), a member of the membrane-bound receptor tyrosine kinase family, is associated with the pathogenesis of a variety of tumors (65). HCG11 and EphA2 are downregulated, while miR-1297 are upregulated in SACC cells. The binding of HCG11 to miR-1297 alleviated the inhibition of EphA2 expression by miR-1297 and EphA2 knockdown reversed the inhibitory effect of HCG11 overexpression on the SACC cell phenotype. These findings indicate that the HCG11/miR-1297/EphA2 regulatory axis in SACC is a promising therapeutic target for SACC (35).

In VS cells, HCG11 expression is low, and overexpression of HCG11 can inhibit proliferation and promote apoptosis (36). *In vivo*, nude mice were used to investigate the effect of HCG11 on OSCC cell growth, and the results revealed that compared with the control group, the HCG11 knockdown group experienced faster tumor growth and greater tumor weight. Further RT-qPCR analysis revealed that the expression of miR-455-5p was increased and that the expression of protein tyrosine phosphatase receptor s (PTPRS) was decreased in tumor tissues in which HCG11 was knocked down, which may provide a new RNA target for the treatment of OSCC (37).

The overexpression of HCG11 can inhibit laryngeal carcinoma (LC) cell proliferation and promote apoptosis, and the mechanism is related to the regulation of the miR-4469/apolipoprotein M (APOM) axis. These findings highlight the potential of HCG11 as a valuable therapeutic target for LC, underscoring its relevance in oncology research (23).

In addition, signal transducer and activator of transcription 3 (STAT3) positively activates HCG11 expression by binding to its promoter region in TC, and HCG11 captures miR-450b-5p through sponge adsorption to promote taste receptor type 2 expression, leading to inhibited cell proliferation and migration, and enhanced ferroptosis in TC cells (38).

Although HCG11 has a tumor suppressive effect on a variety of cancers, it can also exhibit opposite promoting effects under specific circumstances. HCG11 is highly expressed in nasopharyngeal carcinoma (NPC) and positively associated with tumor stage, lymph node metastasis and poor prognosis. Knockdown of HCG11 inhibits the proliferation and migration and induces apoptosis in NPC cells (24). Similarly, in MM cells, HCG11 shows high expression and is notably associated with the OS of patients, and knockdown of HGC11 can inhibit MM cell proliferation (25).

In summary, the dual function of HCG11 as an oncogene or tumor suppressor depends on various factors, such as the cancer type and subtype, expression level, tumor microenvironment, and signaling pathway. This highlights the importance of fully understanding the diverse roles and regulatory pathways within the framework of complex cancer biology. In addition, an in-depth understanding of the interactions between HCG11 and other signaling pathways, miRNAs and proteins is essential for understanding the role of HCG11 in the initiation and progression of various cancers and for improving related diagnostic and therapeutic approaches.

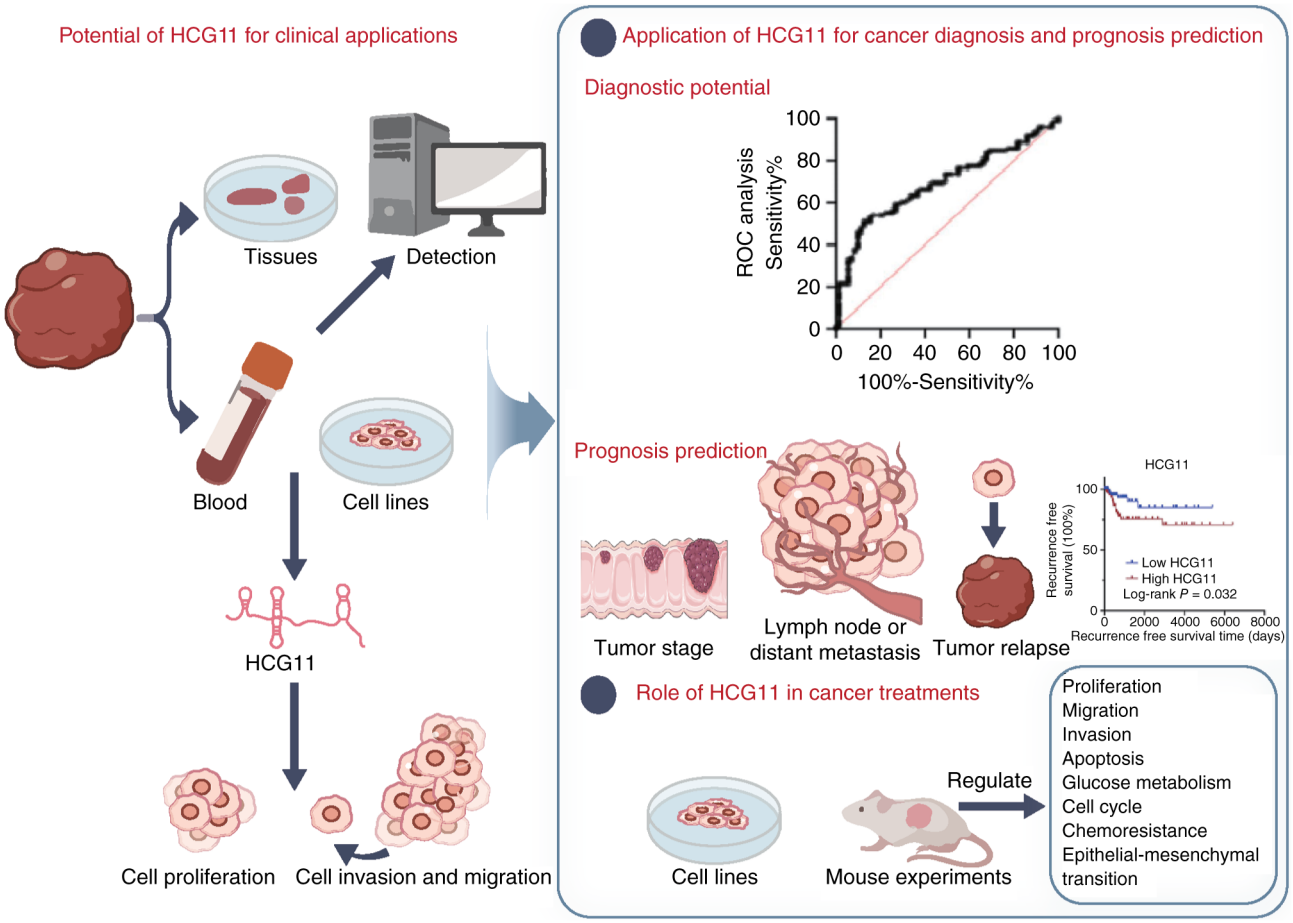

Figure 4. Clinical relevance and functional mechanisms of HCG11 in human cancers. On the left, HCG11 can be detected in tumor tissues and blood samples, and its dysregulation regulates core malignant phenotypes of cancer cells, including proliferation, invasion and migration. On the right, the diagnostic value of HCG11 validated by ROC curve analysis and its prognostic significance correlated with tumor stage, metastasis, recurrence and recurrence-free survival is shown. The functional effects of HCG11 on cancer progression, including its roles in proliferation, invasion, apoptosis, metabolism, and chemoresistance, as supported by *in vitro* and *in vivo* experiments, are presented. HCG11, HLA complex group 11; lncRNA, long non-coding RNA.

3. Potential clinical application of HCG11 in cancer

Tumor-related molecular markers are crucial for cancer detection, treatment and prognosis. Common biomarkers, such as carcinoembryonic antigen (CEA), a-fetoprotein (AFP) and cancer antigen 19-9 (CA 19-9), face limitations in terms of their specificity and sensitivity for cancer diagnosis and prognosis (66,67). Consequently, the identification and exploration of novel markers have substantial clinical relevance. A recent study demonstrated that lncRNAs are abundant in human cancer tissues and blood, emerging as a new focus for biomarkers in cancer diagnosis, prognosis and treatment due to their inherent detectability and specificity (68). Likewise, HCG11 is crucial for the advancement of various cancer types and shows considerable potential as a biomarker for forthcoming diagnostic, therapeutic and prognostic applications (Fig. 4).

HCG11 as a potential diagnostic biomarker in cancers. It has been shown that lncRNAs circulate unchecked in plasma and that their expression levels are almost identical to those in primary tumor tissues. These lncRNAs can clearly reflect the characteristics of the corresponding tumors (69). Empirical evidence suggests that HCG11 has good potential as a diagnostic biomarker for various malignancies. Notable abnormalities in HCG11 levels have been observed in a variety of cancer tissue specimens, differentiating them from healthy individuals (10,12,21). Compared with healthy tissues, the expression level of HCG11 in NSCLC tissues was 5.11 times higher than that in adjacent normal tissues. In addition, according to receiver operating characteristic (ROC) analysis, the area under curve (AUC) of HCG11 was 0.63, the sensitivity was 69%, the specificity was 57%, the positive predictive value (PPV) was 54.72% and the negative predictive value (NPV) was 58.1%, indicating a moderate diagnostic potential for HCG11 in NSCLC (70). Chemotherapy and radiotherapy are the main methods of CRC treatment. Compared with before chemotherapy, the AUC of HCG11 in patients with CRC and healthy groups was 0.690 (sensitivity=69%; specificity=56%; P<0.0001), indicating that HCG11 has the potential as a diagnostic marker for CRC (42).

The distinctive stability of lncRNAs and their resilience against degradation enable them to maintain both their structural and functional integrity for extended periods within the circulatory system, positioning them as potential biomarkers for cancer (71). Although HCG11 expression levels can be used to separate tumor tissues from normal tissues and can be measured in serum to distinguish patients with cancer from

healthy individuals, some restrictions exist that hinder its application in clinical work. First, HCG11 has low specificity. The abnormal expression of HCG11 has been observed in numerous types of malignant tumors; hence, this finding indicates that HCG11 is not a biomarker that is specific to tumors. When it is used alone, it is not able to exactly distinguish one single kind of cancer. Second, non-tumor diseases, including inflammation reactions, benign lesions and individual differences, may influence the expression of HCG11. This circumstance can cause false-positive or false-negative results upon clinical inspection. Furthermore, the majority of current research depends upon a restricted sample size and single-center data. Currently, there are no large-scale, multicenter clinical verification studies; therefore, this leads to the instability of the diagnostic effect. In addition, the expression of HCG11 differs greatly across tumor subtypes; therefore, this further reduces its specificity in clinical work. Therefore, when HCG11 is used to carry out tumor diagnosis, it must be combined with traditional serum tumor markers such as CEA, AFP and CA19-9 to increase diagnostic specificity and accuracy. Studies that have higher standardization and larger sample sizes are therefore needed to overcome these limitations.

HCG11 as a therapeutic target in cancer. HCG11 participates in various processes associated with different cancers, such as proliferation, apoptosis, migration, invasion and EMT, by competing with the ceRNA machinery. To date, to the best of our knowledge, there have been no clinical trials specifically targeting HCG11, but studies on its function and molecular mechanism in a variety of tumors have laid the foundation for clinical treatment. Several experiments have shown that HCG11 serves a role as an oncogene or tumor suppressor gene in CRC, HCC, NSCLC, PCa, CC, EC, osteosarcoma, MM, TC and VS. Targeted therapy is a therapeutic strategy that targets specific molecular targets in cancer cells and aims to address the disadvantages of low specificity and notable toxicity associated with radiotherapy and chemotherapy.

The extreme specificity of lncRNAs makes them suitable therapeutic targets (72). On the basis of preclinical studies, it is not difficult to alter HCG11 expression *in vivo* by viral vectors or non-viral delivery, which may provide new opportunities for targeted cancer therapy. Stably transfected A490 cells were inoculated subcutaneously into BALB/c nude mice, and HCG11 overexpression decreased the tumor volume and weight of NSCLC (19). Through xenograft experiments, Mao *et al* (20) also reported that HCG11 overexpression inhibited tumor growth and that HCG11 silencing promoted tumor growth *in vivo*; these effects could be reversed by LATS1 silencing and overexpression, respectively. These data reveal that HCG11 inhibits NSCLC tumor growth through LATS1 *in vivo*. In the same OSCC nude mouse xenograft model, HCG11 knockdown resulted in faster tumor growth and greater tumor weight (37). However, inhibition of HCG11 expression in nude mice transfected with AGS cells markedly reduced the tumor volume in patients with GC (16). Similarly, in a mouse xenograft model, overexpression of HCG11 also notably reduced tumor weight and size in BRCA (17).

Resistance during chemotherapy poses a great challenge for CRC treatment. Improving sensitivity to chemotherapy is key to improving its efficacy (73). To clarify the mechanism of drug resistance in CRC, studies have shown that HCG11 expression is increased in 5-FU-resistant CRC and promotes 5-FU resistance in colon cancer cells by targeting the miR-144-3p-PDK4 axis to reprogram glucose metabolism (27). These findings open new avenues for the treatment of patients with CRC who are resistant to chemotherapy in the clinical setting.

HCG11 as a prognostic marker in cancers. Prognostic assessment serves a crucial role in assessing the treatment status of patients and adjusting treatment plans in a timely manner. HCG11 has been widely shown to be critical for modulating prognosis. In PCa, Kaplan-Meier survival curves revealed that the 5-year biochemical recurrence (BCR)-free survival rate of patients with low HCG11 expression was markedly lower than that of patients with high HCG11 expression, and multivariate Cox regression analysis revealed that HCG11 was an independent prognostic factor for PCa (P=0.047) (12). Low expression of HCG11 is associated with tumor size, TNM stage and lymph node metastasis in patients with NSCLC (18). However, survival curve analysis revealed that the 5-year survival rate of patients in the high-HCG11 expression group was notably lower than that in the low-HCG11 expression group, and high expression of HCG11 was positively associated with the TNM stage of HCC (10).

DNA methylation is an important epigenetic mechanism that controls the expression of oncogenic or tumor suppressor genes and has potential prognostic relevance in cancer (74). Zeng *et al* (75) reported that HCG11 is a methylation driver gene and that its expression level is negatively associated with methylation; moreover, patients with low HCG11 expression have markedly shorter OS, indicating poor prognosis. In cervical cancer (CC), univariate Cox regression analysis revealed that high expression of HCG11 was notably associated with poor recurrence-free survival (RFS) (P=0.032), and multivariate Cox regression analysis also confirmed that HCG11 was an independent risk factor for CC recurrence (P=0.029) (76). In osteosarcoma and glioma, HCG11 is associated with tumor size and poor prognosis (14,21). HCG11 is highly expressed in NPC tissues and is positively associated with tumor stage, lymph node metastasis and poor prognosis, suggesting that HCG11 has the potential to become an important prognostic marker for patients with NPC (24). These findings highlight that HCG11 may be a promising prognostic biomarker for multiple cancer types. Continuous monitoring of HCG11 levels is helpful for evaluating the severity of malignant tumors and observing their progression.

4. Molecular mechanism of HCG11 in cancer

The role of HCG11 in tumors can be classified into three types: ceRNA activity, pathway involvement and protein interactions.

Acting as ceRNAs. The ceRNA hypothesis has attracted notable interest in the field of RNA biology, revealing novel mechanisms through which RNA species interact (77). lncRNAs serve as a molecular sponge for miRNA, thus influencing gene expression, and are essential within the ceRNA network (78). As illustrated in Fig. 5, HCG11 contributes to various human cancers by modulating the expression of its downstream target genes through competitive interactions with miRNAs.

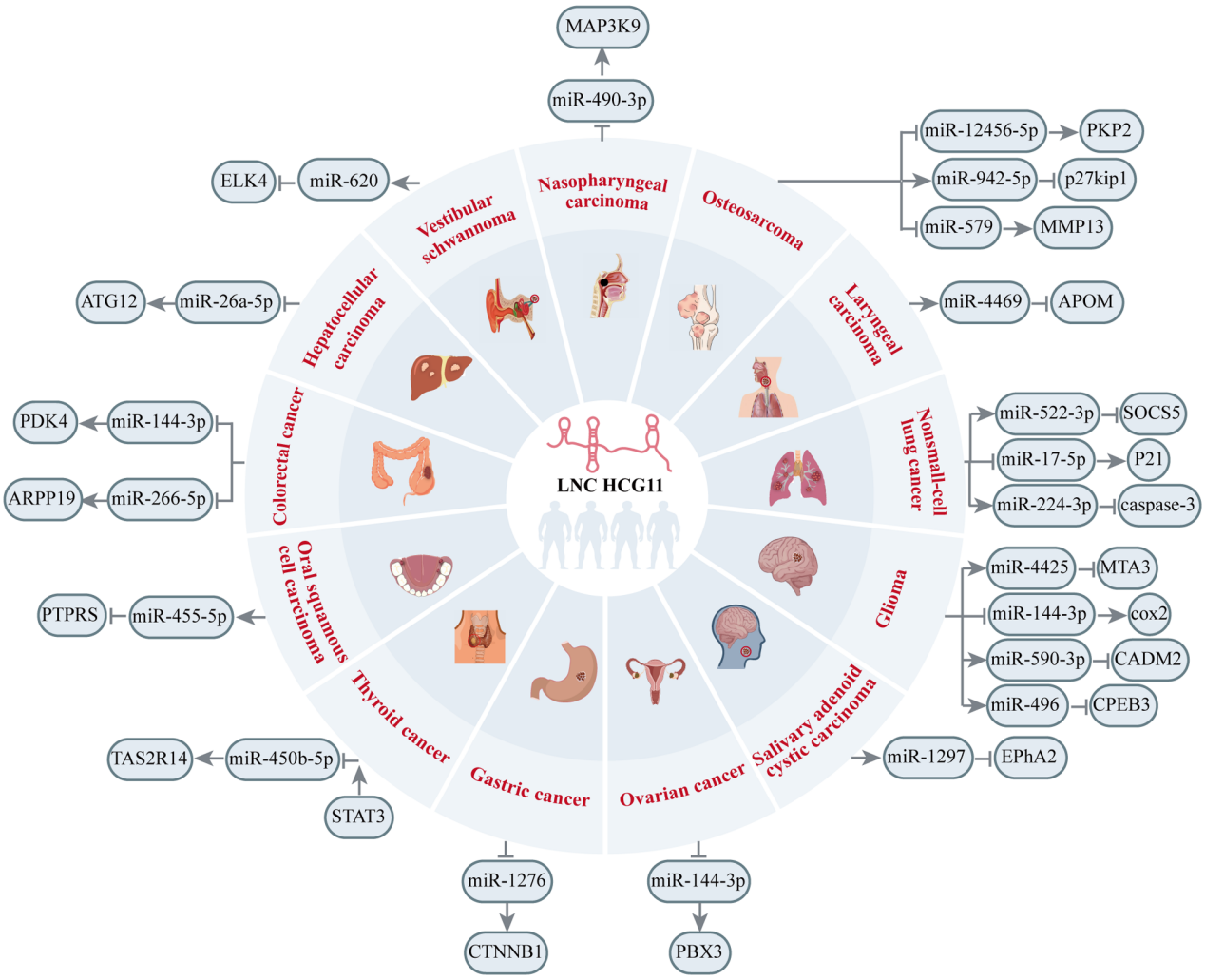

Figure 5. Schematic of the lncRNA-miRNA-mRNA regulatory network of HCG11 in human cancers. HCG11, HLA complex group 11; lncRNA, long non-coding RNA; miRNA/miR, microRNA.

HCG11 expression is elevated in 5-FU-resistant CRC. Silencing HCG11 inhibits CRC cell proliferation, migration, invasion and glucose metabolism and sensitizes CRC cells to 5-FU. Further mechanistic studies revealed that HCG11 promotes 5-FU resistance in CRC cells by targeting the miR-144-3p-PDK4 axis to reprogram glucose metabolism (27). Guo *et al* (26) reported that HCG11 was upregulated in CRC cells and promoted cell proliferation, migration and invasion and inhibited apoptosis by targeting the miR-26b-5p/ARPP19 axis. In HCC, HCG11 accelerates the progression of HCC through the miR-26a-5p/ATG12 axis (10). HCG11 is highly expressed in NPC tissues. Mechanistically, miR-490-3p is the direct target of HCG11. The carcinogenic function of HCG11 in the proliferation and migration of NPC cells is achieved through the inhibition of miR-490-3p and subsequent activation of mitogen-activated protein kinase 9 expression (24). *In vivo* experiments confirmed that HCG11 knockdown could promote the growth of OSCC cells. Mechanistically, HCG11 negatively regulates miR-455-5p, and PTPRS targeted by miR-455-5p regulates the proliferation and growth of OSCC cells (37).

Understanding the mechanism of GEM resistance is highly important for the treatment of NSCLC. Xu *et al* (33) first revealed that HCG11 reversed GEM resistance in NSCLC by regulating the miR-17-5p/p21 axis through a ceRNA mechanism, providing a reference for therapeutic targeting against chemotherapy resistance in NSCLC. In addition, the carcinogenic mechanism in osteosarcoma is related to the HCG11/miR-1245b-5p/PKP2 axis and the HCG11/miR-579/MMP13 axis (21,34). However, the expression levels of HCG11 and the ETS transcription factor ELK4 (ELK4) were low, and the expression of miR-620 was high in VS. HCG11 inhibited the expression of ELK4 through competitive binding to miR-620 to inhibit the growth of VS cells (36). HCG11 is expressed at low levels in LC tissues and cells, while APOM is also downregulated in LC tissues and cell lines; HCG11 positively regulates APOM at the post-transcriptional level, and miR-4469 positively regulates APOM at the post-transcriptional level. The results revealed that HCG11 upregulated the expression of APOM through the absorption of miR-4469 and inhibited the occurrence and progression of LC (23). In glioma, HCG11 acts synergistically with the miR-4425/MTA3 axis to inhibit glioma growth (13).

Involvement in signaling pathways. lncRNAs have key effects on biological responses and gene expression cascades through

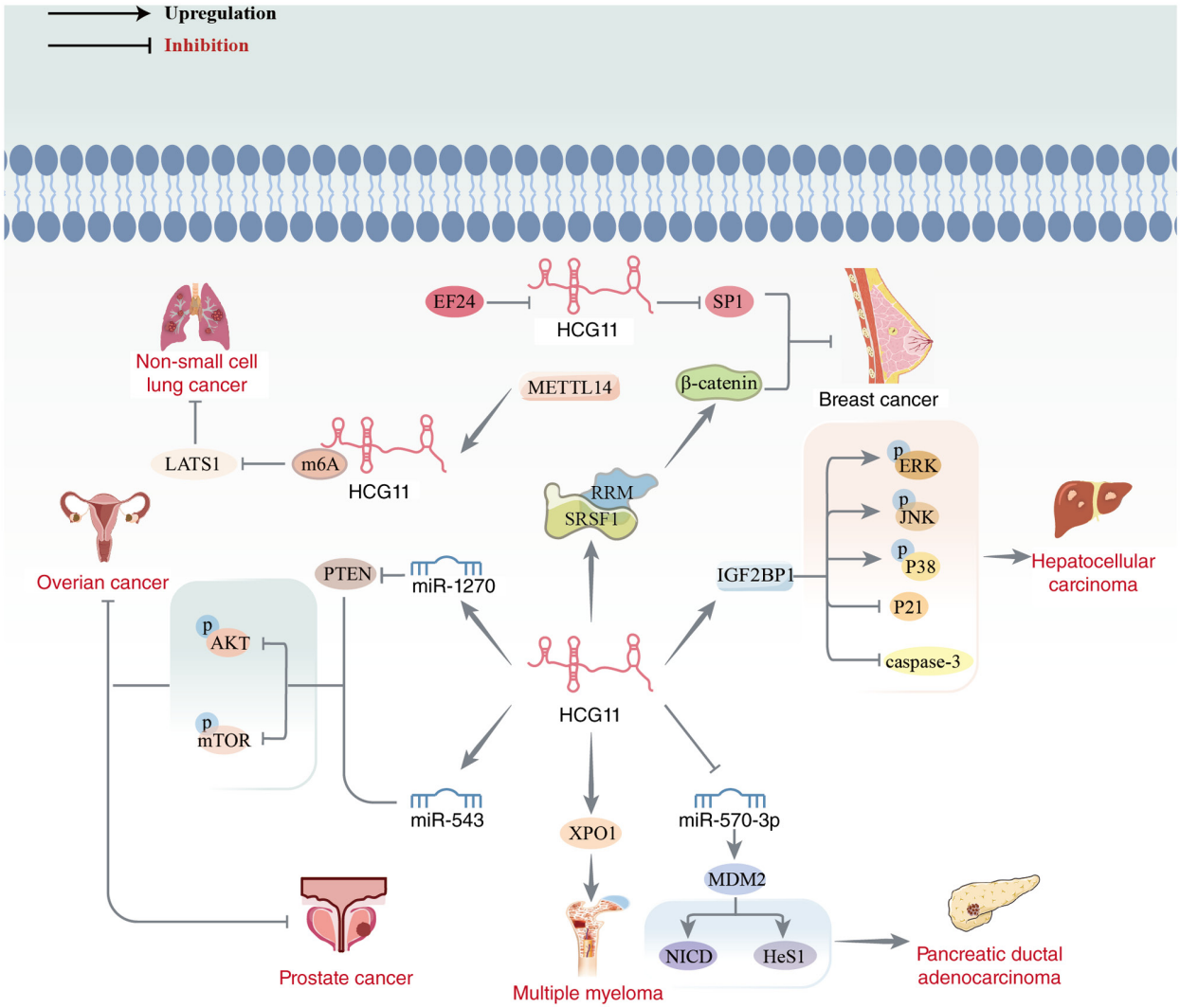

Figure 6. Regulatory mechanisms of HCG11 via protein interactions and classical signaling pathways. HCG11 interacts with multiple functional proteins and modulates the activity of the MAPK, PI3K/AKT and Notch/Hes1 signaling cascades to regulate tumor biological behaviors. HCG11, HLA complex group 11; Hes1, hairy and enhancer of split-1.

various signaling pathways, suggesting that the modulation of specific lncRNAs and their pathways may serve as a viable approach for cancer therapy (79). Multiple lines of evidence implicate HCG11 in cancer development through three signaling cascades: The MAPK, PI3K/AKT and Notch/hairy and enhancer of split-1 (Hes1) pathways (Fig. 6).

The MAPK pathway is a key signal transduction component that translates extracellular stimuli into a wide range of cellular responses, and its abnormal activation is an important cause of the development of a variety of cancers (80). Xu *et al* (11) reported that in HCC, HCG11 further activated the expression of the key anti-apoptotic proteins phosphorylated (p)-ERK, p-JNK and p-P38 in the MAPK signaling pathway by positively regulating the expression of IGF2BP1 and inhibiting the expression of the pro-apoptotic proteins p21 and caspase-3, ultimately driving the malignant progression of HCC.

The PI3K/AKT pathway is important for cell cycle regulation and is related to the occurrence and development of a variety of tumors. p-AKT, AKT, p-mTOR and mTOR are key proteins of the PI3K/AKT/mTOR pathway. Bioinformatics prediction revealed complementary binding sequences between miR-543 and the 3'-UTR of HCG11. In PCa, HCG11 overexpression notably inhibited miR-543 expression, whereas HCG11 knockdown increased miR-543 expression. Furthermore, HCG11 inhibited the expression of P-AKT and p-mTOR, key proteins of the PI3K/AKT signaling pathway, by regulating miR-543 to inhibit the progression of PCa (29). Another study revealed that HCG11 sponged miR-1270 to inhibit PTEN expression, further inhibiting p-AKT and p-mTOR levels and OC development, suggesting that it could be a potential target for OC treatment (32). HCG11, as a ceRNA, directly binds to and adsorbs miR-579-3p and reduces its activity. miR-579-3p directly targets MDM2 and promotes its expression. Furthermore, MDM2 overexpression led to increased expression of key Notch/Hes1 pathway proteins, such as the Notch intracellular domain and Hes1. Ultimately, this promotes the growth and invasion of PC (28).

Interactions between biological proteins and molecules. In addition to its role as a molecular sponge for miRNAs and its

involvement in related signaling pathways, HCG11 is involved in the control of gene transcription and epigenetics through interactions with biomolecules (Fig. 6). HCG11 expression is downregulated in LUAD, and this effect is regulated by HCG11 promoter methylation and methyltransferase-like 14 (METTL14)-mediated N6-methyladenosine (m6A) modification. m6A modification promotes the nuclear export of HCG11 and binding to IGF2BP2. HCG11 can recruit IGF2BP2 to target LATS1 and inhibit LUAD tumor growth. A previous study demonstrated that HCG11, mediated by METTL14, inhibits LUAD growth through the activity of IGF2BP2/LATS1 (20). Both *in vivo* and *in vitro* experiments have demonstrated that HCG11 has a tumor suppressor effect on HR-positive BRCA cells, and its mechanism involves the targeting of β-catenin mRNA by the recruitment of SRSF1, thus promoting the translation of β-catenin (17). HCG11 directly binds and stabilizes exportin-1 (XPO1) mRNA, promotes its translation, leads to XPO1 protein upregulation and mediates MM selinexor resistance. Targeting the HCG11-XPO1 axis may reverse drug resistance (25). In a TNBC xenograft mouse model, the administration of the curcumin analog EF24 reduced tumor volume. In the TNBC cell line, the administration of EF24 reduced cell viability and inhibited cell invasion. Overexpression of HCG11 can restore the proliferation and invasion ability of EF24-inhibited TNBC cells and enhances SP1 expression by reducing its ubiquitination, thus enhancing SP1-mediated cell survival and invasion in TNBC cell lines. Therefore, EF24 treatment reduces HCG11 expression, leading to the degradation of SP1 expression, which inhibits the proliferation and invasion of TNBC cells (60).

5. Discussion and future perspectives

HCG11 is a crucial RNA molecule involved in regulating tumor development and progression. Recent studies have demonstrated its dual role as both a tumor suppressor and an oncogene across various cancer types, emphasizing the intricate nature of cancer mechanisms. HCG11 is vital in several cancers, such as HCC, CRC, OC, VS, PCa, glioma, GC, PC, BRCA, NSCLC, OSCC and SACC, because it influences essential processes such as cell proliferation, migration, invasion, apoptosis, cell cycle arrest, drug resistance and EMT. Furthermore, the expression of HCG11 is clinically relevant in cancer and is associated with factors such as TNM stage, tumor size, lymph node metastasis, tumor invasion and adverse prognosis indicators (including OS, BCR, RFS, PPV and NPV). The role of HCG11 in cancer is multifaceted and involves competitive binding with miRNAs to modulate downstream mRNAs, the activation of three signaling pathways (MAPK, PI3K/AKT and Notch/Hes1) and interactions with various proteins. Moreover, HCG11 levels can be used to differentiate tumor tissues from normal tissues, and its presence in serum can help distinguish between healthy individuals and patients with cancer. Its specificity for tumors and stability in plasma highlight its notable potential as a biomarker for cancer diagnosis, treatment and prognosis.

Although some progress has been made regarding HCG11, the understanding of it is still limited and incomplete. First, although HCG11 is differentially expressed in a variety of tumors, this differential expression is not consistent across different tumors and can even have opposite effects on the same tumor. For example, HCG11 is highly expressed in GC tissues and cells, and its expression level is positively associated with TNM stage. The inhibition of HCG11 can inhibit GC cell proliferation and migration. However, another study revealed that the expression of HCG11 was downregulated in GC cells and that overexpression of HCG11 inhibited the proliferation, migration and invasion of GC cells. Similarly, HCG11 expression was notably upregulated in ER-negative tissues and TNBC, and its upregulation was notably associated with OS. However, HCG11 expression was markedly downregulated in HR-positive tissues and cell lines, and low expression was associated with tumor size. The multiple functions of HCG11 in tumors are shaped by numerous factors, such as tumor subtype, specimen source, detection method and molecular interaction structure. The molecular properties of every subtype and the cell environment determine whether HCG11 functions as a cancer-promoting gene or a tumor-inhibiting gene. The different sample sources, non-unified detection platforms and diverse experimental designs thus lead to inconsistent results.

Notably, the functions of HCG11 are dependent on the surrounding environment. It achieves its function through the sequestration of different miRNA molecules and the modulation of a number of types of downstream target genes and signal conduction pathways. These pathways include the Wnt, PI3K/AKT, MAPK and Notch/Hes1 signaling cascades. Epigenetic regulation, such as promoter methylation and m6A modification, also affects the expression and subcellular localization of HCG11. As a result, its biological function has been altered. Second, previous studies are limited mainly to *in vitro* cell experiments and mouse experiments and lack large-scale clinical cohort verification, especially prospective studies. In addition, the studies focus mostly on a single signaling pathway, and the understanding of the transcriptional regulatory mechanism involved in HCG11, the dynamic structural changes in subcellular localization, other non-coding RNAs involved, and multiple parallel or intersecting networks regulated by HCG11 is insufficient. A deeper understanding of the structural basis and mechanisms underlying the functional diversity of HCG11 could not only expand the understanding of its role in tumor biology but also provide a basis for therapeutic mechanisms and novel markers to guide patient treatment. To obtain a more in-depth understanding of the functional mechanism of HCG11 inside tumors and for advancing its clinical usage, large-scale and multicenter clinical research is necessary. These studies could confirm its importance in early-stage cancer examination, dynamic treatment monitoring and prognosis evaluation among various groups of individuals.

Recently, advancements in liquid biopsy have revealed that lncRNAs that circulate in serum and plasma are very stable. They are protected by extracellular small vesicles or ribonucleoprotein compound bodies and exhibit expression modes that are consistent with those of tumor organization (81). Therefore, they act as very good non-invasive biological markers. As HCG11 is abnormally regulated and has prognostic relevance in numerous types of malignant tumors, the development of standardized and sensitive methods for detecting serum or plasma levels of HCG11 has great potential for non-invasive cancer screening, real-time treatment

assessment and early recurrence prediction. The combination of HCG11 together with traditional serum markers such as CEA, AFP and CA19-9 can increase diagnostic accuracy and therefore overcome the limitations of single markers.

Moreover, there is an urgent need to develop feasible and safe methods to make HCG11-targeted treatment plans clinically applicable. Along with the rapid development of nucleic acid treatment methods, some delivery systems have already shown promising results in clinical practice (82). These contain lipid nanoparticles, engineered exosomes, adeno-associated virus vectors, and chemically altered antisense oligonucleotides or small interfering RNAs. These systems are able to achieve accurate tumor-targeted transmission, as they can either resume the expression of tumor-suppressing HCG11 or downregulate oncogenic HCG11. Surface modification using targeting ligands can further increase tumor specificity, reduce off-target effects and promote *in vivo* bioavailability. Building a classification system of molecules that is based on HCG11 in accordance with cancer type and subtype will therefore aid in personalized detection and accurate treatment. The integration of advanced technologies such as artificial intelligence, single-cell RNA sequencing, spatial transcriptomics and proteomics will help clarify the dynamic regulatory network of HCG11 within the tumor microenvironment. Taken together, these efforts link basic investigation and clinical work, indicating HCG11 is a promising biomarker for use as a liquid biopsy and treatment target for accurate cancer therapy.

In summary, while previous reviews have investigated the effects of HCG11 in specific cancer types, the present review adopts a more comprehensive cross-cancer perspective to elucidate the dual functionality and regulatory mechanisms of HCG11. By unifying molecular mechanisms from >15 different cancer types, new insights into clinical characteristics are revealed. The analysis encompasses clinical factors such as disease progression, metastasis and treatment resistance, in addition to molecular pathways. Advances in science and technology, along with enhanced research methodologies, are anticipated to unlock greater potential for the use of HCG11 in cancer diagnosis, prognosis assessment and therapeutic strategies. However, although this review systematically combs the existing studies, there are still shortcomings. Most of the existing studies are single-center basic experiments and there is a lack of large sample clinical cohort studies. The opposite biological functions of HCG11 in various tumors have not been fully elucidated. In addition, the therapeutic delivery technology targeting regulation of HCG11 is still in the preclinical stage, and its clinical safety and efficacy need to be verified in the long term. Looking forward, it is crucial to further merge fundamental research with clinical practice to translate findings related to HCG11 into tangible medical advancements and to devise improved diagnostic and treatment approaches for patients with cancer.

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Competing interests

The authors declare that they have no competing interests.

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