

## Review Article

# Regulatory mechanisms and potential medical applications of HNF1A-AS1 in cancers

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**Abstract:** Long noncoding RNAs (lncRNAs) are defined as a class of non-protein-coding RNAs that are longer than 200 nucleotides. Previous studies have shown that lncRNAs play a vital role in the progression of multiple diseases, which highlights their potential for medical applications. The lncRNA hepatocyte nuclear factor 1 homeobox A (HNF1A) antisense RNA 1 (HNF1A-AS1) is known to be abnormally expressed in multiple cancers. HNF1A-AS1 exerts its oncogenic roles through a variety of molecular mechanisms. Moreover, aberrant HNF1A-AS1 expression is associated with diverse clinical features in cancer patients. Therefore, HNF1A-AS1 is a promising biomarker for tumor diagnosis and prognosis and thus a potential candidate for tumor therapy. This review summarizes current studies on the role and the underlying mechanisms of HNF1A-AS1 various cancer types, including gastric cancer, liver cancer, glioma, lung cancer, colorectal cancer, breast cancer, bladder cancer, osteosarcoma, esophageal adenocarcinoma, hemangioma, oral squamous cell carcinoma, laryngeal squamous cell carcinoma, cervical cancer, as well as gastroenteropancreatic neuroendocrine neoplasms. We also describe the diagnostic, prognostic, and therapeutic value of HNF1A-AS1 for multiple cancer patients.

**Keywords:** HNF1A-AS1, lncRNA, expression, function, mechanism, cancer biomarker

### Introduction

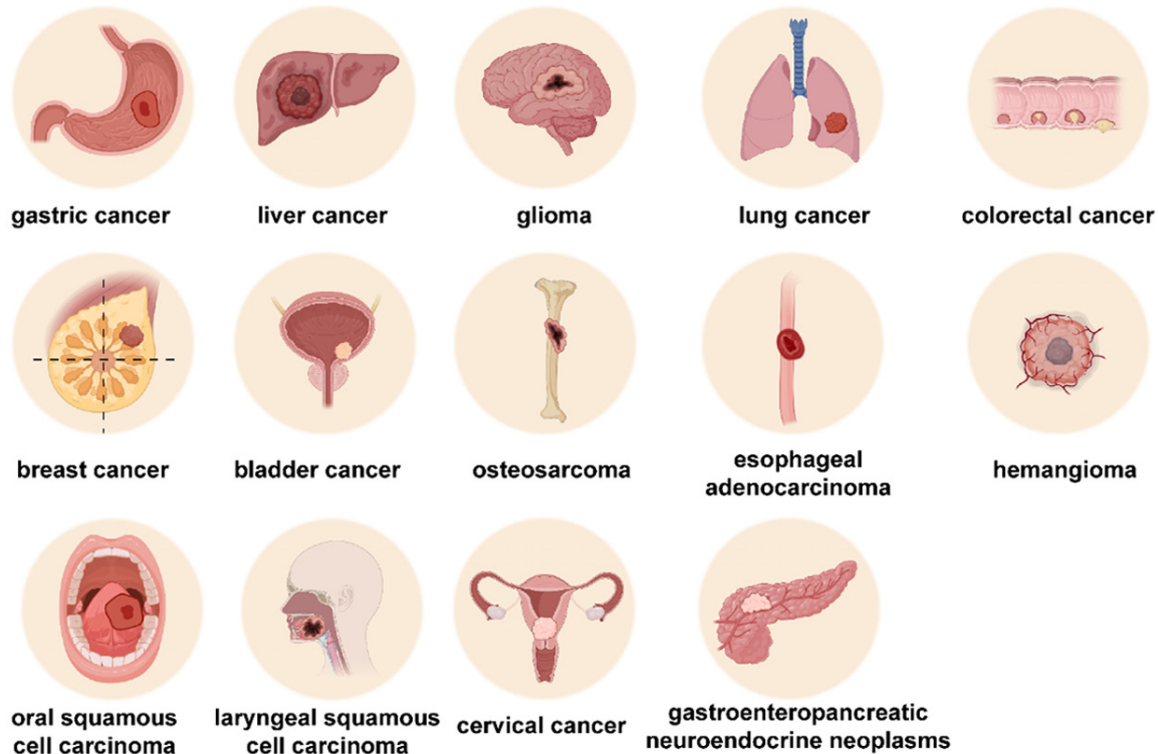
Despite rapid improvements in diagnostic and therapeutic strategies, cancer remains with high incidence and mortality, as well as a low cure rate [1, 2]. An estimated 18.1 million new cancer cases were diagnosed in 2018, associated with nearly 9.6 million deaths across 185 countries, according to the GLOBOCAN 2018 database [3, 4]. Therefore, greater insight into cancer pathogenesis and the identification of reliable biomarkers for early cancer diagnosis and treatment are urgently required [5, 6].

Long noncoding RNAs (lncRNAs) are a type of non-protein-coding RNA with transcripts more than 200 nucleotides in length [7-11]. Increasing evidence has revealed that lncRNAs are closely involved in modulating the progression of multiple diseases, including cancers [12-16]. lncRNAs are known to work as competitive endogenous RNAs (ceRNAs) that inhibit

the expression of mRNA or interact with various protein components, regulating diverse cell biological processes [17-21].

The lncRNA hepatic nuclear factor 1 $\alpha$  (HNF1A) antisense RNA 1 (HNF1A-AS1) [22-25] is an antisense RNA for *HNF1A* located on human chromosome 12q24.31. HNF1A-AS1 is 2455 nucleotides long with a start site approximately 5 kb downstream of *HNF1A*. Emerging studies have revealed that HNF1A-AS1 is dysregulated in many cancers. Furthermore, abnormal HNF1A-AS1 expression has been associated with various cancers. HNF1A-AS1 is also a critical regulator of cancer development by regulating multiple biological processes. Given these properties, HNF1A-AS1 is increasingly recognized as a promising biomarker for diagnosis and prognosis and an attractive therapeutic target for numerous cancers. Here, we summarize current knowledge regarding the roles of HNF1A-AS1 in cancers, which is comprised of

## Functions of HNF1A-AS1 in cancers



**Figure 1.** The involvement of HNF1A-AS1 in different types of cancer. HNF1A-AS1 h cancer and participates in the regulation of the progression of cancer, including gastric cancer, liver cancer, glioma, lung cancer, colorectal cancer, breast as an aberrant expression in various types of c cancer, bladder cancer, osteosarcoma, esophageal adenocarcinoma, hemangioma, oral squamous cell carcinoma, laryngeal squamous cell carcinoma, cervical cancer, and gastroenteropancreatic neuroendocrine neoplasms.

dysregulated expression, associated clinical features, regulatory functions, related molecules, as well as clinical practice.

### The expression and regulatory function of HNF1A-AS1 in cancers

Abnormal HNF1A-AS1 expression has been observed in various types of human cancer, including gastric cancer [24, 26-28], liver cancer [23, 29-31], glioma [32-34], lung cancer [35-39], colorectal cancer [40-44], breast cancer [45-47], bladder cancer [48-50], osteosarcoma [51-53], esophageal adenocarcinoma [25], hemangioma [54], oral squamous cell carcinoma [55], laryngeal squamous cell carcinoma [22], cervical cancer [56, 57], and gastroenteropancreatic neuroendocrine neoplasms (Figure 1) [58]. Additionally, numerous studies have shown that HNF1A-AS1 expression is related to several clinical characteristics of cancer patients, such as tumor size, tumor (T) node (N) and metastasis (M) (TNM) stage, lymph node metastasis (LNM), distant metastasis, di-

sease-free survival, and overall survival (Table 1). HNF1A-AS1 is also involved in regulating diverse cancer cell processes through multiple mechanisms, containing cell proliferation, apoptosis, invasion, migration, glycolysis, cell chemoresistance, as well as radioresistance (Table 2).

We present specific expression profiles, clinicopathological features, and biological roles of HNF1A-AS1 in various cancer types.

#### Gastric cancer

Gastric cancer is one of the commonest types of gastrointestinal malignancies and contributes to the second-highest cancer mortality rate worldwide [59-61]. Despite surgical excision is the primary remedies for early-stage and locally advanced gastric cancer, patients are usually diagnosed at a terminal period that is short of effectual therapies [62-65]. Therefore, exploring highly effective, targeted therapeutic agents for advanced gastric cancers is warranted.

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**Table 1.** The expression and clinical characteristics of HNF1A-AS1 in human cancers

Disease type	Expression	Clinical characteristics	Refs
gastric cancer	upregulated	lymph node metastasis	[26-28]
	downregulated	tumor size, levels of serum carcinoembryonic antigen (CEA), carbohydrate antigen 19-9 (CA19-9), and RRM1 expression	[24]
gastric cancer	upregulated	/	[28]
liver cancer	upregulated	tumor size, tumor stage, multiple lesions, and poor differentiation	[29-31]
	downregulated	/	[23]
glioma	upregulated	overall survival	[32-34]
lung cancer	upregulated	overall survival, pathological stage, TNM stage, tumor size, and lymph node metastasis	[35-39]
colorectal cancer	upregulated	tumor size, TNM stage, lymph nodes metastasis, distant metastasis, overall survival, disease-free survival, and vascular invasion	[40-44]
colorectal cancer	upregulated	/	[88]
breast cancer	upregulated	overall survival	[45-47]
bladder cancer	upregulated	histological grade, TNM stage, lymph nodes metastasis, and overall survival	[48-50]
osteosarcoma	upregulated	clinical stage, distance metastasis, chemotherapy resistance, and poor overall survival	[51-53]
cervical cancer	upregulated	/	[56, 57]
esophageal adenocarcinoma	upregulated	/	[25]
hemangioma	upregulated	/	[54]
oral squamous cell carcinoma	upregulated	nodal invasion, tumor stage, and tissue differentiation	[55]
laryngeal squamous cell carcinoma	downregulated	/	[22]
gastroenteropancreatic neuroendocrine neoplasms	downregulated	/	[58]

Several studies have reported that HNF1A-AS1 may act as an oncogene, with upregulated expression in gastric cancer tissues and cell lines (HGC-27, MKN-45, AGS, NCI-N87, and BGC-823) [26-28]. Additionally, high HNF1A-AS1 expression is correlated with LNM and poor response to 5-fluorouracil (5-FU)-based neoadjuvant chemotherapy. HNF1A-AS1 enhances cell proliferation and invasion, as well as tumor angiogenesis and lymphangiogenesis in mouse tumor xenograft assays. However, Dang et al. [24] demonstrated HNF1A-AS1 downregulation in gastric cancer, with HNF1A-AS1 downregulation associated with tumor size, serum CEA and CA19-9 concentration, and ribonucleotide reductase catalytic subunit M1 (RRM1) expression in tissue samples. Further research is needed to clarify the reasons for differential expression of HNF1A-AS1 in gastric cancer.

### Liver cancer

Hepatocellular carcinoma (HCC) is frequent liver malignancies, with high morbidity and negative prognosis [66-69]. Some studies have shown that HNF1A-AS1 levels are clearly upregulated in HCCMMC-7721, Huh7, MHCC97L, and HepG2 Cells and tissue samples. Fur-

thermore, in these studies, HNF1A-AS1 levels were positively associated with tumor stage, multiple lesions, as well as poor differentiation [29-31]. *In vitro* functional assays demonstrated that HNF1A-AS1 facilitates the proliferation, apoptosis, and autophagy in HepG2, SMCC-7721, and Huh7 cells. However, other studies have shown that HNF1A-AS1 is downregulated and can inhibit the proliferative and metastatic abilities of HCC Huh-7 cells and xenograft tumors [23]. These conflicting results in liver cancer indicate that HNF1A-AS1 expression and function may be affected by tissue and cellular specificity [23]. Further studies with large sample sizes and tissues and cells from multiple sources remain necessary to define the exact roles of HNF1A-AS1 in liver cancer.

### Glioma

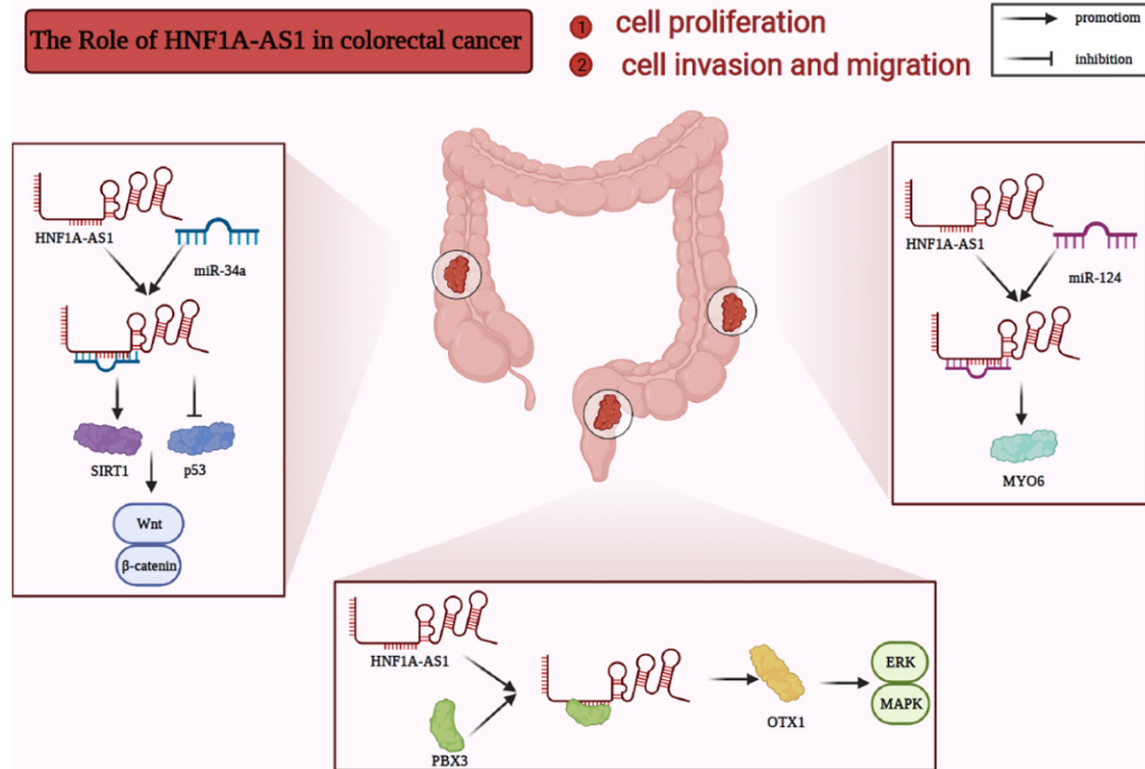
Glioma is an aggressive, intracranial neoplasm associated with high rates of mortality, recurrence, and morbidity [70-74]. Data from the Chinese Glioma Genome Atlas showed that overall survival time remains unfavorable for malignant gliomas, despite advances in neurosurgical techniques [75-77]. HNF1A-AS1 is overexpressed in glioma tissues and LN229,

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**Table 2.** The roles and mechanisms of HNF1A-AS1 in human cancers

Disease type	Role	Cell lines	Functions	Related mechanisms	Refs
Gastric cancer	tumor promoter	HGC-27, MKN-45, AGS, NCI-N87, and BGC-823	cell proliferation, migration, invasion, and 5-FU resistance	miR-30b-5p, EIF5A2, miR-30b-3p, PIK3CD, PI3K, AKT, miR-661, CDC34,	[26-28]
	tumor suppressor	AGS, BGC-823, and MKN-45	/	/	[24]
Gastric cancer	tumor promoter	BGC-823, and MKN-45	cell proliferation, migration, and invasion	EGR1, and miR-661	[28]
liver cancer	tumor promoter	SMMC-7721, MHCC97L, Huh7 and HepG2	cell proliferation, apoptosis, and autophagy	miR-30b-5p, ATG5, EZH2, NKD1, and p21	[29-31]
	Tumor suppressor	Huh-7, MHCC-97L, MHCC-97H, MHCC-LM3, SMMC-7721, and YY-8103	cell proliferation, migration, and invasion	SHP-1	[23]
glioma	tumor promoter	U251, SHG-44, LN229, LN18, U87, T98G, and A172	cell proliferation, apoptosis, migration, and invasion	EGR1, miR-22-3p, ENO1, MYC, miR-32-5p, SOX4, miR-363-3p, MAP2K4, and JNK	[32-34]
lung cancer	tumor promoter	A549, SPC-A1, PC9, H1299, H1563, H1437, H520, H2023, H1650, H1703, SK-MES-1, and Calu-1	cell proliferation, apoptosis, migration, and invasion	miR-92a-3p, MAP2K4, miR-149-5p, Cdk6, miR-17-5p, and DNMT1	[35-39]
colorectal cancer	tumor promoter	LoVo, SW620, HT-29, DLD-1, Ls-174T, HCT 116, and SW480	cell proliferation, migration, invasion, and glycolysis	PBX3, OTX1, ERK, MAPK, miR-124, MYO6, Wnt, $\beta$ -catenin, miRNA-34a, SIRT1, and p53	[40-44]
colorectal cancer	tumor promoter	HT-29, HTC116, RKO, and SW480	/	/	[88]
breast cancer	tumor promoter	MDA-MB-453, MDA-MB-231, MDA-MB-468, MDA-MB-436, MCF-7, BT-20, BT549, ZR-75-30, and HCC1937	cell proliferation, apoptosis, migration, invasion, and TAM resistance	GATA1, miR-32-5p, RNF38, miR-363, SERTAD3, TGF- $\beta$ , Smad, miRNA-20a-5p, and TRIM32	[45-47]
bladder cancer	tumor promoter	T24, J82, UMUC3S, W780, SV-HUC-1, and 5637	cell proliferation, apoptosis, migration, and invasion	miR-101-3p, and Bcl-2	[48-50]
osteosarcoma	tumor promoter	U2OS, SAOS-2, 143B, HOS, SOSP-9607, and MG63	cell proliferation, apoptosis, migration, and invasion	miR-32-5p, HMGB1, Wnt, and $\beta$ -catenin	[51-53]
cervical cancer	tumor promoter	HeLa/DDP	cell proliferation, apoptosis, and cisplatin resistance	/	[56, 57]
esophageal adenocarcinoma	tumor promoter	jhu-esoad1, FLO-1, SKGT-4, and OE33	cell proliferation, and migration	H19, chromatin and nucleosome assembly	[25]
hemangioma	tumor promoter	endothelial cells	cell proliferation, migration, and invasion	/	[54]
oral squamous cell carcinoma	tumor promoter	CAL-27, HN5, SCC-15, SCC-9, and Tca8113	cell proliferation, apoptosis, migration, and invasion	STAT3, and Notch	[55]
laryngeal squamous cell carcinoma	Tumor suppressor	TU-177, AMC-HN-8, TU-686, and 293T	cell proliferation, migration, and invasion	/	[22]
gastroenteropancreatic neuroendocrine neoplasms	Tumor suppressor	QGP-1, and STC-1	cell proliferation, migration, and invasion	TCF3, and Oncostatin M	[58]

## Functions of HNF1A-AS1 in cancers



**Figure 2.** HNF1A-AS1 promotes colorectal cancer cell migration, invasion, and proliferation. In colorectal cancer, HNF1A-AS1 enhances cell proliferation, invasion, and migration by repressing miR-34a/SIRT1/p53 signaling and activating the Wnt/β-catenin signaling pathway; interacting with PBX3 and increasing OTX1 to activate the ERK/MAPK pathway; or sponging miR-124 and upregulating MYO6.

LN18, U251, SHG-44, U87, T98G, and A172 cells and is correlated with lower overall patient survival. Elevated HNF1A-AS1 strengthened glioma cell proliferation, metastasis, as well as suppressing apoptosis in A172, U87, U251 and LN18 cells as well as in xenograft mouse models [32-34].

### Lung cancer

Lung cancer generally causes the death of cancer patients, with a 5-year survival rate of less than 20% worldwide [78-81]. The development of an effective approach for early lung cancer detection has been a top research priority for decades [82-84]. HNF1A-AS1 expression is increased in-tumor tissues and SPC-A1, A549, PC9, H1299, H1563, H1437, H520, H2023, H1650, H1703, SK-MES-1, and Calu-1 cells [35-39]. Additionally, HNF1A-AS1 expression interferes with patients' unfavorable overall survival, advanced pathological stage, and LNM. HNF1A-AS1 has pro-lung cancer functions by regulating cell proliferation, cell apoptosis, invasion, and migration in H1563,

SKMES1, A549, PC9, and SPC-A1 cells and promoting tumor growth in mouse xenograft models.

### Colorectal cancer

The incidence of colorectal cancer, a common digestive tract malignancy, has been continuously increasing worldwide [4, 85-87]. HNF1A-AS1 level is increased in colorectal cancer tissue samples and LoVo, SW620, HT-29, DLD-1, Ls-174T, HCT 116, and SW480 cells [40-44, 88]. Additionally, patients with higher HNF1A-AS1 levels are linked to poor disease-free survival, later TNM stage, LNM, overall survival, and vascular invasion. Additionally, HNF1A-AS1 enhances cell proliferation, migration, invasion, and glycolysis in HT29, HCT116, and SW620 cells, as well as in *in vivo* xenograft mouse models (Figure 2).

### Breast cancer

Breast cancer remains the most prevalent cancer in women [89-92]. Early detection and diag-

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nosis of breast cancer improves the patient outcomes and survival rates [93-96]. Several studies have indicated that HNF1A-AS1 is up-regulated in breast cancer tissues and cell lines, including MDA-MB-453, MDA-MB-231, MDA-MB-468, MDA-MB-436, MCF-7, BT-20, BT549, ZR-75-30, and HCC1937 cells [45-47]. Additionally, high HNF1A-AS1 levels are significantly associated with lower breast cancer patient survival [46]. HNF1A-AS1 promotes cell proliferation, apoptosis, migration, invasion, and tamoxifen (TAM) sensitivity in MDA-MB231, MCF-7, MDA-MB-436, BT474, and BT-20 cells. Furthermore, HNF1A-AS1 oncogenic functions were further confirmed on the xenograft mouse model.

### *Bladder cancer*

The early diagnosis and intervention are expected to greatly improve bladder cancer patient survival rates. HNF1A-AS1 is also over-expressed in bladder cancer [97-101]. Not surprisingly, highly expressed HNF1A-AS1 is positively related to histological grade, TNM stage, LNM, and overall survival time [48-50]. Furthermore, HNF1A-AS1 promotes cell proliferation, migration, and invasion and blocks apoptosis in T24, 5637, SW780, and UM-UC-3 cells.

### *Osteosarcoma*

Osteosarcoma is a common primary aggressive bone tumor of children and adolescents [102-106]. HNF1A-AS1 expression is increased on osteosarcoma tissue samples and 143B, HOS, U2OS, SAOS-2, SOSP-9607, and MG63 cells [51-53]. Furthermore, highly expressed HNF1A-AS1 is strongly correlated with poor clinical stage, distant metastasis, chemotherapy resistance, and poor overall survival. Functional experiments revealed that HNF1A-AS1 stimulates cell proliferation, migration, and invasion, in addition to repressing apoptosis in HOS, MG63, Saos-2, and U2OS cells.

### *Other cancers*

Many other types of cancer are affected by HNF1A-AS1. HNF1A-AS1 expression is increased in cervical cancer tissues and cisplatin (DDP)-resistant (HeLa/DDP) cells. Furthermore, HNF1A-AS1 is involved in suppressing cell apoptosis, inducing cell proliferation, and promoting cisplatin resistance [56, 57]. HNF1A-

AS1 is upregulated in esophageal adenocarcinoma tissues [25], as well as in JH-EsoAd1, FLO-1, SKGT-4, and OE33 cells. HNF1A-AS1 also acts as an oncogene by promoting cell proliferation and migration in the esophageal adenocarcinoma cell lines SKGT-4 and OE33. HNF1A-AS1 overexpression promotes cell proliferation, migration, and invasion in hemangioma tissues and endothelial cells [54]. Additionally, HNF1A-AS1 expression is significantly higher in oral squamous cell carcinoma tissues as well as CAL-27, HN5, SCC-15, SCC-9, and Tca8113 cells than adjacent normal tissues and cell lines [55]. HNF1A-AS1 overexpression in Tca8113 and SCC-15 cells enhances cell proliferation and migration, restrains cell apoptosis, and is associated with aggressive nodal invasion, tumor stage, and tissue differentiation. By contrast, HNF1A-AS1 is decreased in laryngeal squamous cell carcinoma tissue samples, cell lines (TU-177, AMC-HN-8, TU-686, and 293T) [22], and metastatic tumors of cervical lymph nodes. Experimental data suggest that HNF1A-AS1 represses cell proliferation and metastasis in TU-177 and TU-686 cell lines and suppresses tumor growth, epithelial-mesenchymal transition, and LNM in *in vivo* xenograft models. Moreover, HNF1A-AS1 is decreased in gastroenteropancreatic neuroendocrine neoplasm tissues and cells (QGP-1 and STC-1) and plays key roles in inhibiting proliferation, migration, and invasion [58].

### **The oncological mechanisms of HNF1A-AS1 in human cancers**

HNF1A-AS1 is involved in a variety of tumor cell processes that affect cell proliferation, apoptosis, invasion, migration, glycolysis, and drug resistance. We next probe the HNF1A-AS1 oncological mechanisms for the major biological functions of diverse cancers.

#### *Cell proliferation*

The dysregulation of cell proliferation is the main hallmark of cancer. Therefore, an in-depth understanding of cell proliferation can ultimately provide insight into cancer development [107-110]. HNF1A-AS1 modulates cell proliferation, including gastric cancer [28], liver cancer [23, 30, 31], glioma [32-34], lung cancer [35-37, 39], colorectal cancer [42-44], breast cancer [45-47], bladder cancer [49, 50], osteosarcoma [51-53], cervical cancer [56], esophageal

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adenocarcinoma [25], hemangioma [54], oral cancer [55], laryngeal cancer [22], and gastroenteropancreatic neuroendocrine neoplasms [58].

In gastric cancer, HNF1A-AS1 is activated by early growth response 1 (EGR1) and binds to microRNA (miR)-661 (miR-661), further elevating the expression of ubiquitin-conjugating enzyme E2 R1 (CDC34) and contributing to the acceleration of cell proliferation in both MKN-45 and BGC-823 cells [28]. HNF1A-AS1 promotes the proliferation of the HCC SMCC-7721 and Huh7 cell lines by combining with histone-lysine N-methyltransferase EZH2 (EZH2) and either downregulating the protein expression of naked cuticle homolog 1 (NKD1) and cyclin-dependent kinase inhibitor 1 (p21) and sponging miR-30b-5p, which enhances autophagy protein 5 (ATG5) expression [30, 31]. HNF1A-AS1 also suppresses Huh-7 cell proliferation by directly interacting with tyrosine-protein phosphatase non-receptor type 6 (SHP-1) [23]. In the glioma cell lines U87-MG, U251, LN18, and A172, HNF1A-AS1 enhances cell proliferation through the EGR1/HNF1A-AS1/miR-22-3p/enolase 1 (ENO1) axis, the myc proto-oncogene protein (MYC)/HNF1A-AS1/miR-32-5p/transcription factor SOX-4 (SOX4) axis, and the MYC/HNF1A-AS1/miR-363-3p/MAP kinase 4 (MAP2K4)/c-Jun N-terminal kinase (JNK) axis [32-34]. HNF1A-AS1 also boosts the proliferative abilities of lung cancer SKMES1, H1563, SPC-A1, A549, PC9, as well as Calu-1 through the miR-92a-3p/MAP2K4/JNK pathway, the miR-149-5p/Cdk6 axis, the DNA (cytosine-5)-methyltransferase 1 (DNMT1)/cyclin D1 axis [35-37, 39], and in combination with miR-17-5p. Additionally, HNF1A-AS1 facilitates proliferation in colorectal cancer cell lines HT29, HCT-116, and SW620 by activation of the Wnt/ $\beta$ -catenin and by inhibiting miR-34a/sirtuin 1 (SIRT1)/cellular tumor antigen p53 (p53) pathway and subsequently activating Wnt [42-44]. HNF1A-AS1 also plays a pro-proliferative role in breast cancer MDA-MB231, and BT474, by incorporating erythroid transcription factor (GATA1), sponging miR-32-5p, upregulating E3 ubiquitin-protein ligase RNF38, integrating with miR-363 to increase SERTA domain-containing protein 3 (SERTAD3) levels, as well as acting on miRNA-20a-5p to elevate E3 ubiquitin-protein ligase TRIM32 [45-47]. HNF1A-AS1 also

sponges miR-101-3p and increases the level of apoptosis regulator Bcl-2 (Bcl-2), promoting cell proliferation in 5637, T24, SW780, and UM-UC-3 bladder cancer cell lines [50]. Additionally, HNF1A-AS1 heightens proliferation in osteosarcoma cell lines HOS, MG63, and U2OS by interacting with miR-32-5p and increasing high mobility group box 1 (HMGB1) expression and by triggering Wnt/ $\beta$ -catenin [52, 53]. In esophageal adenocarcinoma, HNF1A-AS1 may be involved in chromatin and nucleosome assembly or in the modulation of H19 to enhance cell proliferation in SKGT-4 and OE33 cells [25]. In the oral squamous cell carcinoma cell lines SCC-15 and Tca8113 [55], STAT3 upregulates HNF1A-AS1, and HNF1A-AS1 subsequently activates the Notch signaling pathway, exerting pro-proliferative functions. HNF1A-AS1 enhances cell proliferation by mediating the microRNA-34b/TUFT1 axis in DDP-resistant cells [56], which has implications for cervical cancer. Additionally, HNF1A-AS1 induced by IL-6 weakens miR-363-3p expression, which advances the process of hemangioma endothelial cell proliferation [54]. In gastroenteropancreatic neuroendocrine neoplasms and STC-1 and QGP-1 cell lines, HNF1A-AS1 exerts anti-proliferative functions by activating transcription factor 3, subsequently inhibiting Oncostatin M and stimulating the transforming growth factor-beta (TGF- $\beta$ ) signaling pathway [58].

### *Cell migration and invasion*

Aberrant cell metastasis are crucial for cancer progression [111-115]. HNF1A-AS1 affects cell migration and invasion in gastric cancer [27, 28], liver cancer [23], glioma [32, 33], lung cancer [35-37, 39], colorectal cancer [40-44], breast cancer [47], bladder cancer [49], osteosarcoma [51-53], esophageal adenocarcinoma [25], hemangioma [54], oral cancer [55], laryngeal cancer [22], and gastroenteropancreatic neuroendocrine neoplasms [58].

In the gastric cancer, HNF1A-AS1 induces cell migration and invasion by sponging miR-30b-3p and upregulating the phosphoinositol 3-kinase (PI3K)/AKT pathway or by interacting with miR-661 and increasing the expression of CDC34 after activation by EGR1 [27, 28]. By contrast, HNF1A-AS1 blocks metastasis in the

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HCC cell line Huh-7 by functioning as phosphatase accelerators of SHP-1 [23]. HNF1A-AS1 can be activated by MYC, interacting with miR-32-5p to raise SOX4 levels, and activated by EGR1, influencing the miR-22-3p/ENO1 axis to promote cell invasion in glioma cell lines A172, U87, U251, and LN18 [32, 33]. In several lung cancer cell lines, HNF1A-AS1 facilitates the processes of cell migration and invasion through various mechanisms. In A549 and Calu-1 cells, HNF1A-AS1 facilitates the processes of cell migration and invasion by blocking miR-92a-3p and positively modulating the expression of MAP2K4. Furthermore, HNF1A-AS1 inhibits the expression of miR-17-5p in PC9 and A549 cells. Additionally, HNF1A-AS1 sponges miR-149-5p and upregulates Cdk6 in H1563 and SKMES1 cells [35-37]. In colon cancer, HNF1A-AS1 displays pro-metastatic functionality by binding to pre-B-cell leukemia transcription factor 3 (PBX3) and increasing homeobox protein OTX1 (OTX1) to activate the extracellular signal-regulated kinase 1/2 (ERK)/mitogen-activated protein kinase (MAPK) pathway by competitively combining with miR-124 and upregulating unconventional myosin-VI (MYO6), or by crippling the miR-34a/SIRT1/p53 axis and enhancing Wnt in HCT-116 and SW620 cells [40-42, 44]. HNF1A-AS1 accelerates migration and invasion in breast cancer cell lines MDA-MB231 and MCF-7 by sponging miR-20a-5p and upregulating TRIM-32 expression [47]. Through different mechanisms, HNF1A-AS1 boosts cell migration and invasion in osteosarcoma cell lines. In MG63 and U2OS cells, HNF1A-AS1 binds to miR-32-5p, elevating HMGB1 expression. Furthermore, HNF1A-AS1 also promotes the Wnt/ $\beta$ -catenin signaling pathway in HOS and MG-63 cells [52, 53]. In esophageal adenocarcinoma, HNF1A-AS1 is hypothesized to affect cell migration in SKGT-4 and OE33 cells by modulating chromatin and nucleosome assembly as well as H19 induction [25]. In the oral squamous cell carcinoma cell lines SCC-15 and Tca8113, HNF1A-AS1 enhances migration and invasion by the activation of the Notch signaling pathway [55], mediated by STAT3-linked upregulation of HNF1A-AS1. In hemangioma cell lines, IL-6 increases HNF1A-AS1 expression, which accelerates cell migration and invasion by sponging miR-363-3p [54].

### Clinical significance of HNF1A-AS1 in cancer management

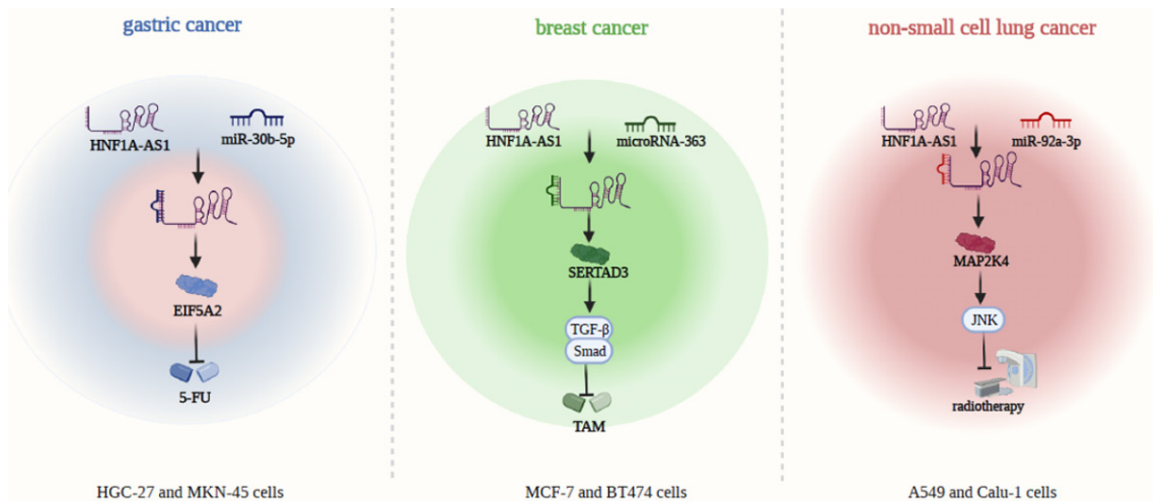
#### *The diagnostic and prognostic value of HNF1A-AS1*

Given the shortage of reliable diagnostic and prognostic biomarkers, the prognosis of cancer patients remains poor. Several findings demonstrate that HNF1A-AS1 levels of cancer cells and tissue samples are highly significant for the clinical diagnosis and prognosis of cancers evaluated by receiver operating characteristic (ROC) curve analysis, Kaplan-Meier analysis, or univariate and multivariate analyses.

For example, HNF1A-AS1 is regarded as a biomarker in gastric cancer for predicting LNM and is able to distinguish patients with LNM from those without with 0.7650 AUC value [27]. Further supporting the powerful diagnostic abilities of HNF1A-AS1, the AUC value of HNF1A-AS1 has been reported as high as 0.8714 in colorectal cancer [42]. Additionally, Kaplan-Meier [40], univariate, and multivariate analyses [44] suggest colon cancer patients with higher HNF1A-AS1 levels have unsatisfactory prognostic outcomes and higher disease relapse rates, further validating the prognostic potential of HNF1A-AS1. The diagnostic value of HNF1A-AS1 was also validated in cervical cancer by ROC curve analysis, with an AUC of 0.774 [57]. Univariate and multivariate analyses [38, 48, 53] have shown HNF1A-AS1 can represent an independent marker of poor prognosis in non-small cell lung cancer, bladder cancer, and osteosarcoma ( $P < 0.05$ ). More importantly, HNF1A-AS1 expression in serum correlates with patient status, revealing that HNF1A-AS1 has more effective diagnostic value than alkaline phosphatase (ALP) for differentiating osteosarcoma patients from healthy cases, with a high AUC value of 0.849 [52]. Blood specimens have several advantages, including easy availability, reduced trauma, lower risk, and high cost-effectiveness associated with sample collection compared with obtaining a cell or tissue biopsy, making blood samples convenient for long-term and continuous monitoring of cancer [116-119]. Simple, quantitative blood assays would provide greater opportunities for cancer identification and earlier intervention and would ultimately increase therapeutic effectiveness [120-124].



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**Figure 3.** HNF1A-AS1-mediated chemoresistance and radioresistance in cancers. HNF1A-AS1 increases 5-FU resistance in the gastric cancer HGC-27 and MKN-45 by sponging miR-30b-5p and upregulating EIF5A2. HNF1A-AS1 also enhances TAM resistance in breast cancer cell lines MCF-7 and BT474 via reducing miR-363 and promoting SERTAD3 expression to activate the TGF- $\beta$ /Smad pathway. In-lung cancer cells, HNF1A-AS1 strengthened radiotherapy resistance of A549 and Calu-1 cells by modulating the miR-92a-3p/MAP2K4/JNK pathway.

Research has focused mostly on HNF1A-AS1 expression in cancer tissues and cells, which is limited for several inherent factors, such as trauma, complicated operation, and high cost, making it unsuitable for early disease diagnosis and the evaluation of disease prognosis. Further study is required to investigate HNF1A-AS1 expression as a diagnostic or prognostic biomarker in less invasive biological specimens, such as blood.

### *The therapeutic value of HNF1A-AS1*

HNF1A-AS1 is dysregulated in different cancers and exerts pro-oncogenic or tumor-suppressing effects. Simultaneously, HNF1A-AS1 modulates a wide range of the vital biological processes of cancer through diverse molecular mechanisms, especially resistance to chemotherapy and radiotherapy (**Figure 3**). Based on the above characteristics, upregulating or downregulating HNF1A-AS1 expression as well as targeting HNF1A-AS1-related molecules and pathways may ultimately pave the way for novel cancer treatments.

For example, HNF1A-AS1 reduces tumor cell sensitivity to 5-FU by obstructing miR-30b-5p expression and upregulating eukaryotic translation initiation factor 5A-2 (EIF5A2) in the gastric cancer, suggesting that HNF1A-AS1 knock-out may result in the remission of cell chemore-

sistance [26]. Similarly, in breast cancer cells [46], HNF1A-AS1 increases TAM resistance by sponging miR-363 and promoting SERTAD3 expression to activate the TGF- $\beta$ /Smad pathway. HNF1A-AS1 also impairs the radiotherapy sensitivity of A549 and Calu-1 lung cancer cell lines by regulating the miR-92a-3p/MAP2K4/JNK pathway, suggesting that inhibiting HNF1A-AS1 could strengthen the efficacy of radiotherapy in non-small cell lung cancer [35]. Furthermore, HNF1A-AS1 enhances ritonavir (RTV)-induced hepatotoxicity mainly by influencing cytochrome P450 3A4 (CYP3A4) expression in hepatoma cells, which provides direction for subsequent research and therapeutics based on the mechanisms of RTV-induced liver damage [29]. Although clinical research of HNF1A-AS1 remains in its infancy, it is a promising field of study for further exploring the clinical value of HNF1A-AS1 in non-invasive cancer detection, prognosis, diagnosis, and treatment effectiveness.

### **Conclusion**

HNF1A-AS1 expression is dysregulated in diverse cancer types, including gastric cancer, liver cancer, glioma, lung cancer, colorectal cancer, breast cancer, bladder cancer, osteosarcoma, esophageal adenocarcinoma, hemangioma, oral cancer, laryngeal cancer, cervical cancer, and gastroenteropancreatic neuroen-

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ocrine neoplasms. Furthermore, HNF1A-AS1 is correlated with a series of clinical characteristics, including TNM stage, tumor size, lymphatic and distant metastasis, and disease-free and overall survival. HNF1A-AS1 participates in multiple critical biological processes in cancer cells by regulating cell proliferation, invasion, and migration, all of which can affect cancer development. Therefore, HNF1A-AS1 could be utilized in promising medicinal applications for cancer, such as diagnosis, prognosis, and treatment.

Altogether, we currently have a rudimentary understanding of the functions and applicational value of HNF1A-AS1 in cancers. Further research into the mechanisms and clinical applications of HNF1A-AS1 is warranted to assess the expression, stability, and presence of HNF1A-AS1 in non-invasive bodily fluids, as well as the effectiveness and safety of targeted-HNF1A-AS1 therapies.

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### Disclosure of conflict of interest

None.

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