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Review

Hepatocyte nuclear factor 1A-antisense: Review of its role in the carcinogenesis

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ABSTRACT

Hepatocyte nuclear factor 1A-antisense (*HNF1A-AS*) is an RNA gene classified as a long non-coding RNA (lncRNA). This gene is located on 12q24.31 and produces at least seven transcripts. This lncRNA contributes in the pathogenesis of cancer via HNF1A-dependent and –independent routes. Moreover, the role of this lncRNA in this process is context-dependent. The bulk of evidence from cell line, in vivo and clinical studies propose HNF1A-AS as an oncogenic lncRNA. However, in hepatic cancer, gastric cancer and laryngeal cancer, opposite results have been reported. In the current review, we explain the impact of HNF1A-AS in the pathoetiology of cancers. In order to appraise the importance of available evidence on this topic, we have classified evidence to preclinical models (cell liens and animal models) and investigations in tissues obtained from human subjects.

1. Introduction

As an RNA gene, *Hepatocyte nuclear factor 1A-antisense* (*HNF1A-AS*) is affiliated with the long non-coding RNA (lncRNA) entity. This class of transcripts has attained much attention during the recent decade, based on their impact on almost all aspects of cell/human life. They have sizes more than 200 bp and can participate in the dynamic modification of chromatin configuration, as well as regulation of genes at transcriptional and post-transcriptional phases. Diverse mechanisms have been found to mediate these effects; among them is their interaction with other RNA types. Moreover, via acting as decoys, scaffolds, and enhancer transcripts, lncRNAs modulate expression levels of genes [6].

Based on the GRCh38/hg38, *HNF1A-AS* gene is located on minus strand of chr12:120,888,868–120,980,965 (12q24.31) and has 92,098 bases. Ensembl database has listed seven transcripts for this gene, named as HNF1A-AS1–204, HNF1A-AS1–205, HNF1A-AS1–207, HNF1A-AS1–201, HNF1A-AS1–203, HNF1A-AS1–206 and HNF1A-AS1–202 with sizes of 2455, 343, 1144, 718, 659, 557 and 546 bps, respectively. Except for the first one which has retained intron, other are classified as lncRNA (http://asia.ensembl.org/Homo_sapiens/). The largest transcript (HNF1A-AS1–207, ENST00000647473.1) has five exons. HNF1A-AS is transcribed from the antisense stand of *HNF1A* gene, which encodes a monomer contributing in the construction of a liver-enriched transcription factor. HNF1A participates in the pathoetiology of some disorders, including cancers [8,20]. Accordingly, the antisense transcript from this locus is mainly involved in the carcinogenic processes. HNF1A-AS1 is only detected in primates. Its transcription has been shown to be activated by HNF1α [4]. In the current review, we explain the impact of HNF1A-AS in the pathoetiology of cancers. In order to appraise the importance of available evidence on this topic, we have classified evidence to preclinical models (cell liens and animal models) and investigations in tissues obtained from human subjects.

2. Literature search

We used PubMed and Google Scholar for finding research articles published up to June 2021. The following keywords were used for literature search: Hepatocyte nuclear factor 1A-antisense, HNF1A-AS, tumor and cancer. The title and abstract of all obtained papers were appraised for relevance. After this step, we excluded irrelevant papers, all types of articles except original research articles and non-English articles. Subsequently, the reference lists of the obtained papers were

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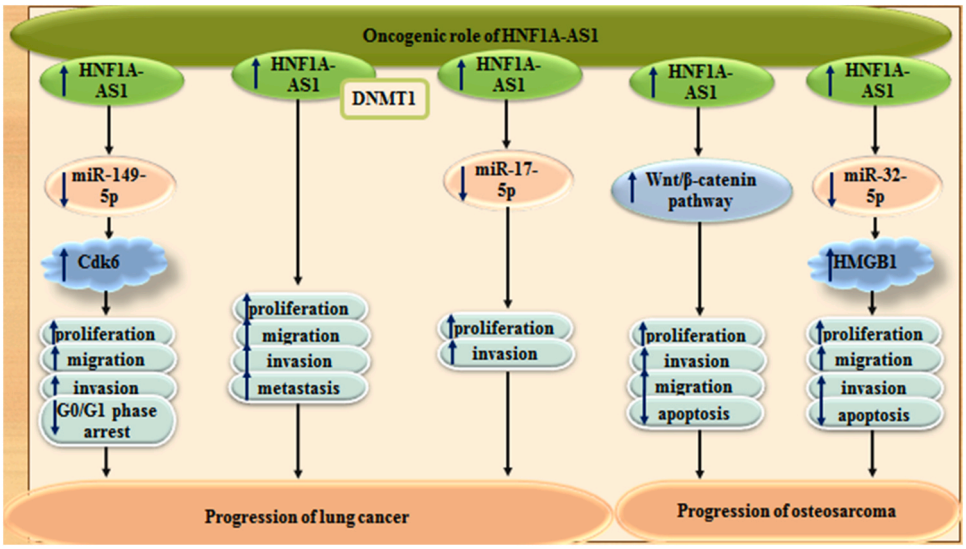

Fig. 1. Role of HNF1A-AS in the pathoetiology of lung cancer and osteosarcoma.

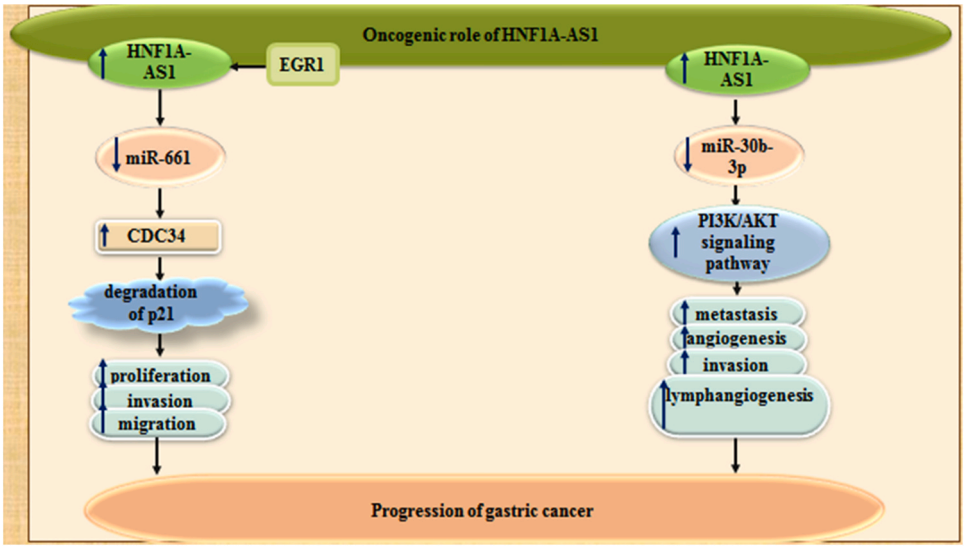

Fig. 2. Role of HNF1A-AS in the pathoetiology of gastric cancer.

assessed to find further relevant articles.

3. Cell line investigation

In esophageal cancer, HNF1A-AS1 silencing has remarkably repressed cell proliferation and anchorage-independent growth, blocked cell cycle transition at G1/S phase, and suppressed their migratory potential and invasion. HNF1A-AS1 silencing has been found to preferentially influence expression of genes that are associated with chromatin assembly and nucleosomes. Notably, H19 lncRNA has been demonstrated as the most noticeably inhibited gene by HNF1A-AS1 silencing. Cumulatively, up-regulation of HNF1A-AS1 contributes in esophageal tumorigenesis, at least partly through regulation of chromatin and nucleosome assemblage and activation of H19 expression [27].

In lung cancer cells, HNF1A-AS1 has been shown to enhance tumor proliferation and metastatic aptitude through modulation of expression of cyclin D1, E-cadherin, N-cadherin and β-catenin. Its regulatory role on E-cadherin can be explained by its binding to DNMT1 [24].

In osteosarcoma cells, HNF1A-AS1 has ben shown to promote cell proliferation and metastatic aptiude via induction of the Wnt/β-catenin signaling pathway [30]. Moreover, it partakes in the pathogenesis of this cancer through regulation of the miR-32–5p/HMGB1 axis [15]. Fig. 1 summarizes the role of HNF1A-AS in the pathoetiology of lung cancer and osteosarcoma.

Moreover, HNF1A-AS silencing has inhibited proliferation and migration capacities of CNE-2 and SUNE-1 nasopharyngeal carcinoma cell lines [32]. Similarly, in gastric cancer cells, HNF1A-AS1 has been shown to promote invasiveness and metastatic ability. Functionally, HNF1A-AS1 serves as a competing endogenous RNA (ceRNA) for miR-30b-3p, resulting in up-regulation of the key oncogene PIK3CD [11]. Another experiment in gastric cancer cells has shown the pro-proliferative role of HNF1A-AS1 and its role in enhancement of cell cycle transition. Notably, expression of this lncRNA has been reported to be activated by early growth response protein 1 (EGR1). HNF1A-AS1 acts as a ceRNA for miR-661, thus increasing expression of its target, i.e. cell division cycle 34 (CDC34). HNF1A-AS1 also increases levels of CDK2, CDK4, and cyclin E1, while suppressing p21 levels through enhancing CDC34-related ubiquitination and degradation of p21 [10]. Fig. 2 shows the role of HNF1A-AS in the pathoetiology of gastric cancer.

In colorectal cancer cells, up-regulation of HNF1A-AS1 has increased

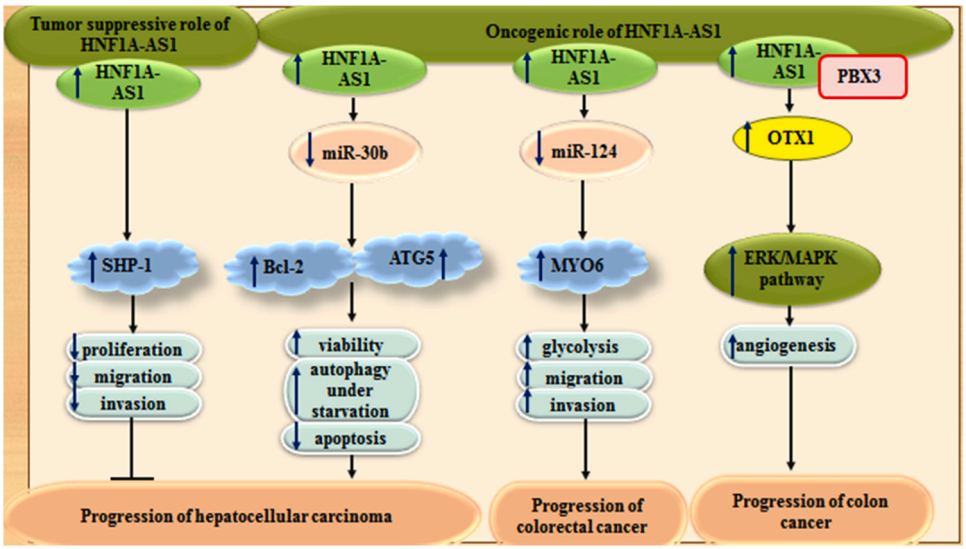

Fig. 3. Role of HNF1A-AS in the pathoetiology of hepatocellular carcinoma and colorectal cancer.

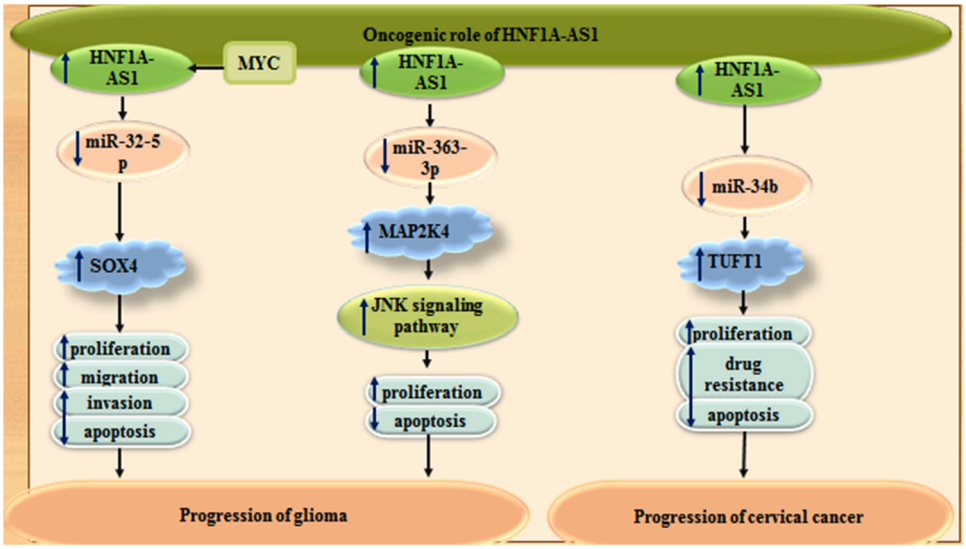

Fig. 4. Role of HNF1A-AS1 in glioma and cervical cancer.

cell viability, migratory potential and invasiveness. Mechanistically, HNF1A-AS1 functions as a ceRNA for miR-34a to regulate SIRT1/p53 axis, leading to induction of canonical Wnt signaling [5].

Conversely, experiments in hepatocellular carcinoma cells have shown that HNF1A-AS1 inhibits the malignant features of these cells and contribute to the anti-tumor influences of HNF1α. Notably, HNF1A-AS1 mediates the regulatory effects of HNF1α on SHP-1 activation in human hepatocellular carcinoma cells and enhances the phosphatase function of SHP-1, Thus, HNF1A-AS1 has a tumor-suppressor role in this type of cancer via modulating the enzymatic activity of SHP-1 [4]. Contrary to this experiment, Liu et al. have demonstrated the oncogenic role of HNF1A-AS1 in hepatocellular carcinoma. They have revealed that HNF1A-AS increases autophagy in these cells via acting as a ceRNA for hsa-miR-30b-5p [14]. Fig. 3 shows the role of HNF1A-AS in the pathoetiology of hepatocellular carcinoma and colorectal cancer.

In glioma cells, expression of HNF1A-AS1 has ben found to be activated by MYC. This lncRNA promotes evolution of glioma via regulating miR-32–5p/SOX4 axis [22]. Moreover, HNF1A-AS1 can activate JNK signaling in these cells through modulation of miR-363–3p/MAP2K4 axis [1]. In cervical cancer cells, HNF1A-AS1 increases resistance to cisplatin via modulating miR-34b/TUFT1 axis [16]. Fig. 4 shows the role of HNF1A-AS1 in glioma and cervical cancer.

HNF1A-AS1 has a role in progression of breast cancer through modulating miR-20a-5p/TRIM32 axis [18]. Moreover, in triple-negative breast cancer cells, HNF1A-AS1 had been found to act as a ceRNA for miR-32–5p to increase level of RNF38 [26]. In bladder cancer, the oncogenic impact of HNF1A-AS is exerted through sequestering miR-30b-5p [28]. Finally, in oral squamous cell carcinoma cells, transcription of HNF1A-AS1 is induced by STAT3. This lncRNA has been shown to activate Notch signaling pathway in oral squamous cell carcinoma [13]. Fig. 5 shows the role of HNF1A-AS in breast, bladder and oral squamous cell carcinomas.

Finally, in laryngeal squamous cell carcinoma cells, HNF1A-AS1 has been displayed to inhibit proliferation, migration and invasiveness of through modulation of the process of epithelial-mesenchymal transition (EMT), suggesting a tumor suppressor role for this lncRNA in this type of carcinoma. Moreover, the migratory and invasive aptitudes, and transcript amounts of HNF1A-AS1 and EMT markers have been reduced by the DNA methylation inhibitor agent 5–Aza-2′-deoxycytidine [19]. Table 1 shows the results of in vitro experiments about the function of

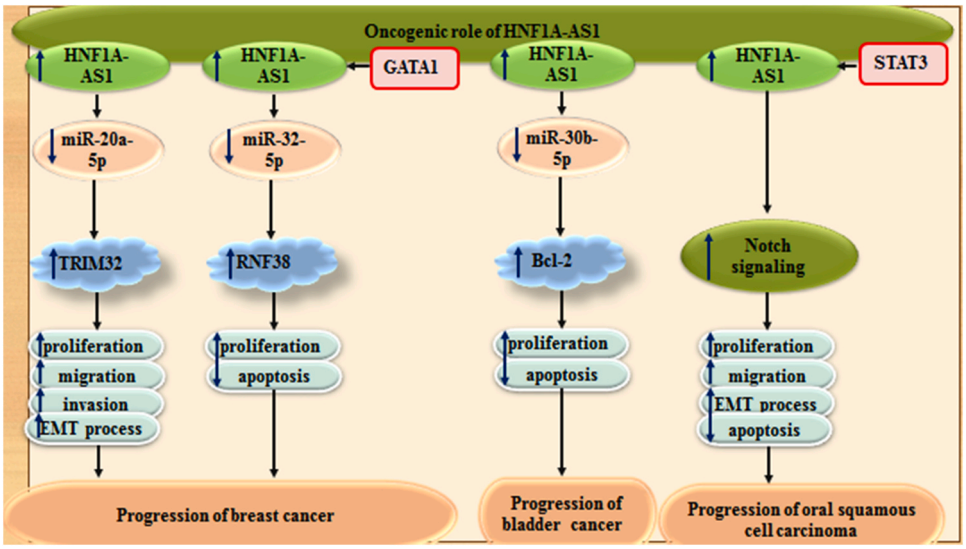

Fig. 5. Role of HNF1A-AS in breast, bladder and oral squamous cell carcinomas.

HNF1A-AS in cancers.

4. Animal studies

In a xenograft model of nasopharyngeal carcinoma, HNF1A-AS silencing has resulted in the suppression of tumor growth and accumulation of cells in the G0/G1 phase. Besides, HNF1A-AS has been shown to participate in the EMT [32]. HNF1A-AS1 has also been shown to promote invasiveness, metastatic ability, angiogenesis and lymphangiogenesis of gastric cancer in animal models [11]. In colorectal cancer cells, up-regulation of HNF1A-AS1 has increased cell viability, migratory potential and invasiveness. HNF1A-AS1 silencing has attenuated growth and metastatic ability of tumor cells in xenograft models [5]. In cervical cancer, HNF1A-AS1 knock-down has enhanced the cytotoxic effects of cisplatin [16].

In an effort to appraise the effects of HNF1A-AS on progression of liver cancer, Ding et al. have injected HNF1A-AS1-overexpresing Huh-7 cell or control cells into the nude mice. Over-expression of this lncRNA has significantly attenuated tumor growth in xenograft models. Moreover, HNF1A-AS1 up-regulation has resulted in smaller tumor nodules and reduced tumor weight compared with the controls. HNF1A-AS1 up-regulation has significantly reduced cell proliferation in xenograft models [4].

Moreover, another in vivo study has shown that HNF1A-AS1 inhibits tumor growth and metastatic ability of laryngeal squamous cell carcinoma through regulating EMT [19]. Table 2 shows the results of animal studies in this field.

5. Clinical studies

HNF1A-AS1 has been found to be up-regulated in lung cancer samples compared with matched non-cancerous tissues. Most notably, expression of HNF1A-AS1 has been correlated with TNM stage, tumor dimension, and lymph node involvement. Moreover, patients with HNF1A-AS1 up-regulation have been shown to experience poor overall survival [24]. In gastric cancer cells, up-regulation of HNF1A-AS1 has been associated with positive lymph node metastasis [11].

In laryngeal squamous cell carcinoma tissues as well as metastatic cervical lymph node specimens, HNF1A-AS1 has been found to be down-regulated as a result of hypermethylation in CpG sites [19]. Table 3 shows the outlines of clinical studies on the role of HNF1A-AS in cancer.

6. Discussion

HNF1A-AS is an lncRNA whose transcription has been shown to be activated by HNF1α [4], a transcription factor with both tumor suppressor and oncogenic activities [8,20]. Moreover, its expression can be reduced through DNA methylation of CpG islands [19]. The bulk of evidence from cell line, in vivo and clinical studies proposes HNF1A-AS as an oncogenic lncRNA. However, in hepatic cancer, gastric cancer and laryngeal cancer, opposite results have been reported. In gastric cancer, while two functional studies have validated the oncogenic roles of HNF1A-AS [10,11], a single study has described down-regulation of HNF1A-AS in cancerous tissues compared with non-cancerous counterparts [3]. In hepatocellular carcinoma, independent functional studies have reported tumor suppressor role [4] and oncogenic role [14] for this lncRNA, with the former effect being also verified in animal models [4]. Finally, in laryngeal squamous cell carcinoma, HNF1A-AS has been found to be a tumor suppressor by a single study [19].

Functionally, HNF1A-AS acts as a ceRNA for miR-661, miR-30b-3p, miR-149–5p, miR-17–5p, miR-32–5p, miR-363–3p, miR-34b, miR-124 and miR-20a-5p. The functional effects of HNF1A-AS on miR-32–5p and miR-30b have been verified by independent studies. HNF1A-AS can regulate activity of PI3K/AKT, Wnt/β-catenin, JNK, TGF-β and Notch pathways. Moreover, it can modulate activity of both apoptosis- and autophagy-related genes.

Few studies have assessed mechanisms that cause the dysregulation of HNF1A-AS in human cancers. Altered levels of HNF1α and modifications in epigenetics marks in the promoter of this lncRNA are possible underlying mechanism of this observation.

Almost all studies in clinical samples have shown association between up-regulation of HNF1A-AS and poor clinical outcomes. Moreover, up-regulation of HNF1A-AS has been associated with a number of clinical parameters delineating malignant features of tumors, such as tumor size, invasion depth or lymphatic/venous/perineural/distant metastasis. Although this lncRNA has been found in cancer-derived exosomes [16], no study has assessed the application of these exosomes as diagnostic/prognostic tools in clinical setting. Thus, future studies should appraise this aspect in order to find non-invasive methods for cancer diagnosis or patients' follow-up.

Although animal studies have reported promising results of the HNF1A-AS-targeting strategies in attenuation of tumor growth, based on the possible tissue-specific roles of this lncRNA, translation of these results into clinical use needs further experiments.

Taken together, HNF1A-AS is an lncRNA with important but dual

Table 1
In vitro experiments about the function of HNF1A-AS in cancers.

Tumor type	Targets/ Regulators and Signaling Pathways	Cell line	Function	Reference
Gastric cancer	miR-661, EGR1, p21, CDC34	MKN-45, BGC-823	↑ HNF1A-AS1: ↑ proliferation, ↑ colony formation, ↑ migration, ↑ invasion, ↑ cell cycle progression Δ HNF1A-AS1: ↓ proliferation, ↓ migration, ↓ invasion	[10]
	miR-30b-3p, PI3K/AKT signaling pathway	MKN-45, BGC-823	Δ HNF1A-AS1: ↓ migration, ↓ invasion ↑ HNF1A-AS1: ↑ migration, ↑ invasion, ↑ angiogenesis, ↑ lymphangiogenesis	[11]
Lung cancer	miR-149–5p, Cdk6	BEAS-2B, H1563, SKMES1, H1299, H1437, A549, H2023	Δ HNF1A-AS1: ↓ Proliferation, ↓ migration, ↓ invasion, ↑ G0/G1 phase arrest ↑ HNF1A-AS1: ↑ proliferation, ↓ G0/G1 phase arrest	[12]
	DNMT1	A549, SPC-A1, H1650, H1703, SK-MES-1, H520, 16HBE	Δ HNF1A-AS1: ↓ Proliferation, ↓ migration, ↓ invasion	[24]
	miR-17–5p	H1299, H1650, A549, and PC9, 16HBE	Δ HNF1A-AS1: ↓ Proliferation, ↓ invasion	[29]
Osteosarcoma	Wnt/β-catenin signaling pathway	HOS, SaOS2, MG63, U2OS, hFOB1.19	Δ HNF1A-AS1: ↓ Proliferation, ↓ migration, ↓ invasion, ↑ apoptosis	[30]
	miR-32–5p, HMGB1	U2OS, Saos-2, 143B, HOS, MG63, hFOB1.19	Δ HNF1A-AS1: ↓ Proliferation, ↓ migration, ↓ invasion, ↑ apoptosis	[15]
	_	HOS, U2OS, SAOS-2, MG63, SOSP-9607, 143B, hFOB1.19, NHOst	Δ HNF1A-AS1: ↓ Proliferation, ↓ migration, ↓ invasion, ↓ EMT process	[2]
Glioma	miR-32–5p, SOX4, MYC	LN229, A172, SHG-44, U87, HEB	Δ HNF1A-AS1: ↓ Proliferation, ↓ migration, ↓ invasion, ↑ apoptosis	[22]
	miR-363–3p, MAP2K4, JNK signaling pathway	U87–MG, A172, U251, T98G, NHA	Δ HNF1A-AS1: ↓ Proliferation, ↑ apoptosis ↑ HNF1A-AS1: ↑ proliferation, ↓ apoptosis	[1]
Cervical cancer	miR-34b, TUFT1	HcerEpic, HeLa/S, HeLa/DDP	Δ HNF1A-AS1: ↓ proliferation, ↓ drug resistance, ↑ apoptosis	[16]
Laryngeal squamous cell carcinoma	_	TU-686, AMC-HN-8, TU-177	↑ HNF1A-AS1: ↓ proliferation, ↓ migration, ↓ invasion, ↓ EMT process,↑ G0/G1 arrest	[19]
Hepatocellular carcinoma	SHP-1	Huh-7, MHCC-97 L, MHCC-97 H, MHCC-LM3, SMMC-7721, YY-8103, HepG2, Hep3B, PLC/PRF/5, 293 T	↑ HNF1A-AS1: ↓ proliferation, ↓ migration, ↓ invasion	[4]
	miR-30b, Bcl-2, ATG5	HepG2, SMMC-7721, PLC/PRF/5, Huh7, HL7702	Δ HNF1A-AS1: ↓ viability, ↓ autophagy under starvation, ↑ apoptosis	[14]
Colorectal cancer	miR-124, MYO6	SW620, HT-29, HCT116 and SW480, NCM460	Δ HNF1A-AS1: ↓ migration, ↓ invasion, ↓ glycolysis	[9]
	_	SW480, SW620, DLD-1, HT29, HCT116, Ls-174 T, LOVO	Δ HNF1A-AS1: ↓ proliferation, ↓ colony formation, ↓ migration, ↓ invasion, ↑ G0/G1 phase arrest	[31]
	PBX3, OTX1, ERK/ MAPK pathway	LoVo, SW620, HCT 116, SW480, FHC, HUVEC	Δ HNF1A-AS1: ↓ angiogenesis	[23]
Breast cancer	miR-20a-5p, TRIM32	MDA-MB-231 and MCF-7	Δ HNF1A-AS1: ↓ proliferation, ↓ migration, ↓ invasion, ↓ EMT process	[18]
	miR-32–5p, RNF38, GATA1	MDA-MB-453, MDA-MB-468, MDA-MB-231, BT-20 and MDA-MB-436, MCF-12 F	Δ HNF1A-AS1: ↓ proliferation, ↑ apoptosis	[26]
Bladder cancer	_	T24, J82, UMUC3, 5637, SV-HUC-1	Δ HNF1A-AS1: ↓ migration, ↓ invasion, ↓ viability, ↓ colony formation, ↑ G0/G1 phase arrest	[7]
	miR-30b-5p, Bcl-2	5637, SW780, UMUC3, T24, SV-HUC-1	Δ HNF1A-AS1: ↓ proliferation, ↑ apoptosis ↑ HNF1A-AS1: ↑ proliferation, ↓ apoptosis	[28]
Oral squamous cell carcinoma	STAT3, Notch signaling	CAL-27, HN5, SCC-15, SCC-9, Tca8113, NHOK	Δ HNF1A-AS1: ↓ proliferation, ↓ migration, ↓ EMT process, ↑ G0/G1 phase arrest, ↑ apoptosis	[13]
Oesophageal cancer	H19	HEEpiC, SKGT-4, OE33, FLO-1, JH-EsoAd1	Δ HNF1A-AS1: ↓ proliferation, ↓ migration, ↓ invasion, ↓ anchorage-independent growth, ↓ survival ↑ G1 arrest	[27]
Gastroenteropancreatic neuroendocrine neoplasms	TCF3, TGFβ signaling pathway.	QGP-1, STC-1, HPNE	↑ HNF1A-AS1: ↓ proliferation, ↓ migration, ↓ invasion, ↓ EMT process	[25]

Table 2
Animal studies about the impact of HNFA1-AS in cancer (Δ: knock-down or deletion, DDP: cisplatin).

Tumor Type	Animal models	Results	Reference
Gastric cancer	male Nu/nu athymic nude mice	↑ HNF1A-AS1: ↑ tumor volume, ↑ tumor growth	[10]
		↑ HNF1A-AS1: ↑ invasion, ↑ metastasis, ↑ angiogenesis	[11]
Lung cancer	female BALB/c nude mice	Δ HNF1A-AS1: ↓ tumor volume, ↓ tumor weight, ↓ tumor growth	[12]
	male athymic BALB/c nude mice	Δ HNF1A-AS1: ↓ tumor size, ↓ tumor weight, ↓ tumor growth	[24]
Glioma	male nude mice	Δ HNF1A-AS1: ↓ tumor volume, ↓ tumor weight, ↓ tumor growth	[22]
Cervical cancer	BALB/c nude mice	Δ HNF1A-AS1 + DDP treatment: ↓ tumor volume, ↓ tumor weight	[16]
Laryngeal squamous cell carcinoma	male Bal/Bc nude mice	↑ HNF1A-AS1: ↓ tumor growth, ↓ EMT process, ↓ lymph node metastasis	[19]
Hepatocellular carcinoma	male BALB/c nude mice	↑ HNF1A-AS1: ↓ proliferation, ↓ tumor weight, ↓ metastasis	[4]
Colon cancer	female BALB/c nude mice	Δ HNF1A-AS1: ↓ tumor volume, ↓ tumor weight, ↓ angiogenesis	[23]
Breast cancer	female mice	Δ HNF1A-AS1: ↓ tumor size, ↓ tumor weight	[26]
Gastroenteropancreatic neuroendocrine neoplasms	nude mice	↑ HNF1A-AS1: ↓ tumor volume, ↓ tumor weight	[25]

Table 3
Outlines of clinical studies on the role of HNF1A-AS in cancer (ANCTs: adjacent non-cancerous tissues, OS: Overall survival, TNM: tumor-node-metastasis, UCB: urothelial carcinoma of the bladder).

Tumor type	samples	Expression (Tumor vs. Normal)	Kaplan-Meier analysis (HNFA1-AS up-regulation)	Univariate/ Multivariate cox regression	Association of HNF1A-AS1 expression with Clinicopathologic characteristics	Reference
Gastric cancer (GC)	99 GC samples and 8 non-tumorous gastric tissues	up	_	_	_	[10]
	67 GC tissues and 6 non-tumourous gastric mucosa tissues	up	_	_	lymph node metastasis	[11]
	6 pairs of GC tissues and ANCTs	down	_	_	_	[3]
	161 pairs of GC tissues and ANCTs	down	_	_	tumor size/diameter, invasion depth, lymphatic metastasis, venous invasion, and perineural invasion	
Lung cancer	60 NSCLC tissues and ANCTs	up	short OS	_	advanced TNM stage, big tumor size, lymph node metastasis	[12]
	40 pairs of lung adenocarcinoma tissues and ANCTs	up	worse OS	_	tumor size, TNM stage, and lymph node metastasis	[24]
	53 NSCLC tissues and ANCTs	up	_	_	advanced TNM stage and lymph node metastasis	[29]
	177 NSCLC tissues and ANCTs	up	shorter OS	HNF1A-AS expression, TNM stage, and lymph node status were found to be independent prognostic factors.	lymph nodes metastasis	[17]
Osteosarcoma	43 pairs of cancer tissues and ANCTs	up	poorer OS	Clinical stage, distant metastasis and HNF1A-AS1 expression were independent prognostic factors for OS.	clinical stage and distant metastasis	[30]
	68 pairs of cancer tissues and ANCTs	up	worse OS	_	clinical II and III stages	[15]
	96 pairs of cancer tissues and ANCTs	up	_	_	_	[2]
Glioma	35 glioma tissues and 10 normal tissues	up	_	_	_	[22]
	36 pairs of glioma tissues and ANCTs	up	shorter OS	_	_	[1]
Laryngeal squamous cell carcinoma (LSCC)	30 LSCC tissues and ANCTs	down	_	_	_	[19]
Hepatocellular carcinoma	40 pairs of tumor tissues and ANCTs	up	_	_	_	[14]
Colorectal cancer (CRC)	40 pairs of CRC tissues and ANCTs	up	_	_	_	[9]
	14 pairs of CRC tissues and ANCTs	up	_	_	lymph-node metastasis	[31]
Colon cancer	GEO analysis: 4 pairs of colon cancer tissues and ANCTs (GSE75970)	up	_	_	_	[23]
	98 Colon cancer tissues and ANCTs	up	_	_	_	
Breast cancer	28 TNBC tissues and paired para-tumor tissues	up	_	_	_	[26]
Bladder cancer	30 pairs of cancer tissues and ANCTs	up	_	_	_	[7]
	191 pairs of UCB tumor tissues and ANCTs	up	Poorer OS	Expression of HNF1A-AS1 was independent prognostic factor for patients with UCB.	histological grade, tumor stage T, lymph nodes metastasis	[21]
	79 pairs of cancer tissues and ANCTs	up	_	_	advanced TNM stage	[28]
Oral squamous cell carcinoma (OSCC)	62 pairs of OSCC tissues and ANCTs	up	Poorer OS	_	nodal invasion, T stage, and differentiation	[13]
Gastroenteropancreatic neuroendocrine neoplasms (GEP-NENs)	3 gastric NENs tissues and peri-cancerous tissues	down	_	_	_	[25]

roles in the carcinogenesis process. Future studies are essential to find the mechanisms of such contradictory effects. This issue should be solved before suggestion of HNF1A-AS as a therapeutic target in human cancers. Moreover, it is necessary to find possible mechanisms of a probable tissue-specific or context-specific function of HNF1A-AS.

Declaration of Competing Interest

The authors declare they have no conflict of interest.

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