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Review

A review on the role of NCK1 Antisense RNA 1 (NCK1-AS1) in diverse disorders

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ABSTRACT

NCK1 Antisense RNA 1 (NCK1-AS1), alternatively named as NCK1-DT, is a long non-coding RNA (lncRNA) with important roles in the carcinogenesis. Multiple studies verified its oncogenic role in different types of cancer, including gastric cancer, non-small cell lung cancer, glioma, prostate cancer and cervical cancer. NCK1-AS1 functions as a sponge for several microRNAs, including miR-137, miR-22–3p, miR-526b-5p, miR-512–5p, miR-138–2–3p and miR-6857. In this review we present an outline of NCK1-AS1 function in malignant conditions as well as atherosclerosis.

1. Introduction

Categorized by their absence of translation, long non-coding RNAs (lncRNAs) are a group of RNAs that are principally transcribed by RNA POL II [26]. LncRNAs are usually longer than 200 nucleotides in length and have several cellular functions [26]. The main duty of these molecules is gene expression regulation, which takes place at diverse levels including transcription and post-transcription [26]. According to GENCODE project, there are approximately 16,000 lncRNAs in human genome [5]. Recently, the role of lncRNAs in the pathogenesis of both malignant and non-malignant conditions has been determined [4,9,10,15,25]. For instance, it has been shown that lncRNAs play important roles in cancers and gametogenesis [6,8].

NCK1 Antisense RNA1 (NCK1-AS1), is a lncRNA transcribed from 3q22.3 locus (Fig. 1). According to NCBI, this lncRNA is mainly transcribed in lymph node and spleen (https://www.ncbi.nlm.nih.gov/gene/101927597). According to ensemble genome browser, NCK1-AS1 has 9 transcripts (https://asia.ensembl.org/Homo_sapiens/Gene/Summary?g=ENSG00000239213;r=3:136835345–136862618).

NCK1-AS1 has been shown to be dysregulated in different cancers, especially cervical cancer, non-small lung cancer, glioma and gastric cancer. Dysregulation of NCK1-AS1 affects its downstream targets and contributes to the pathogenesis of diseases. In addition to malignant conditions, NCK1-AS1 is engaged in pathogenesis of atherosclerosis [30].

In this manuscript, we gathered all NCK1-AS1 related studies and reviewed its function in both malignant and non-malignant conditions to provide an overview of its function sin diverse disorders and highlight its role as a biomarker, particularly in cancers.

2. Malignant conditions

2.1. Cell line studies

There have been some informative studies on the role of NCK1-AS1 in vitro. One frequent event in many types of cancer is dysregulation of NCK1-AS1 expression and its effects on miR-137 levels. To begin with, in laryngeal squamous cell carcinoma, knockdown of NCK1-AS1 results

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in reduced transcription of NCK1, an adjacent gene which is up-regulated by NCK1-AS1. This phenomenon occurs because silencing of NCK1-AS1 causes increase in levels of miR-137, a miRNA that targets NCK1 (Fig. 2). Cumulatively, NCK1-AS1 silencing leads to reduced proliferation, migration, invasion, and elevated apoptosis through modulation of expression of miR-137 [27]. The same molecular mechanism applies for ovarian cancer cell lines SNU119, Caov3, SKOV3, OVCAR-3, SUN8 [1]. In ovarian cancer, in addition to hampering malignant features of cells, silencing of NCK1-AS1 reduces DDP (cisplatin) resistance in mentioned cell lines [1].

In gastric cancer cell lines BGC-823 and MGC-803, miR-137 targets NUP43 and contributes to diminished malignant properties of the cells [19]. Identical to the majority of studies, different cellular properties have been determined by cell Counting Kit-8 (CCK-8) assay, colony formation assay, wound healing assay and transwell invasion assay to confirm the oncogenic roles of NCK1-AS1 [19].

NCK1-AS1 knock down leading to increased levels of miR-137 has also hampered malignant features of non-small cell lung cancer cell lines A549, SPC-A-1, SK-MES-1, H1299,95D [18] and osteosarcoma cell lines MG63, KHOS and U2OS [3].

Tripartite Motif Containing 24 (TRIM24) is a transcriptional coactivator with oncogenic role that affects different kinds of genes including STAT3 [23]. Two independent in vitro studies conducted in glioma cell lines have revealed that NCK1-AS1 can regulate TRIM24 levels and contribute to the progression of cancer. In a study by Huang L and colleges, forced reduction of NCK1-AS1 in glioma cell lines U251, SHG-441, U87 and T98 has given rise to elevated levels of miR-138–2–3p [14] which in turn has down-regulated TRIM24. This axis has contributed to the inactivation of Wnt/β-catenin signaling pathway and reversed malignant properties of cells [14]. Compatible with previous studies, silencing NCK1-AS1 in glioma cell lines U251, A172 up-regulates miR-137, reduces TRIM24 levels and switches malignant features to normal behavior and enhances sensitivity to temozolomide [2]. Small interfering (si)RNA-mediated NCK1-AS1 silencing in nasopharyngeal carcinoma (NPC) cells has also led to the over-expression of miR-135a. Both NCK1-AS1 knock-down and miR-135a up-regulation has repressed migration and invasion of mentioned cells. Moreover, miR-135a suppression has attenuated the impacts of NCK1-AS1 knock-down in these cells [13]. Table 1 summarizes the effects of NCK1-AS1 in different cancer lines.

2.2. Animal studies

Analogous to cell lines studies, NCK1-AS1 functions as an oncogenic lncRNA in animal models of cancers and its silencing reduces malignant features in these models. Two different studies in gastric cancer have revealed that downregulating NCK1-AS1 contributes to lower rate of tumor growth and decreased tumor volumes [11,19].

In glioma, after transfecting BALB/C nude mice with LN229 cells containing short hairpin RNA of NCK1-AS1 and comparing it to normal controls, suppressed tumor growth was observed [28]. Another study by Huang L and colleges confirmed that NCK1-AS1 plays an oncogenic role in glioma and its knockdown reduces malignant features [14]. The results of these studies are summarized in Table 2.

2.3. Clinical evaluations

All of the 20 studies conducted on clinical specimens to appraise role of NCK1-AS1 revealed that this lncRNA acts as a transforming gene and is up-regulated in different kinds of cancer (Table 3). As manifested in hepatocellular carcinoma cell lines, over-expression of NCK1-AS1 reduces miR-22–3p levels. This miRNA impairs PI3K/AKT signaling pathway by down-regulating YARS (a tRNA synthetase). In concordance with cell line studies, overexpression of NCK1-AS1 has been detected in HCC tissues compared with adjacent normal tissues. Patients with over-expressed NCK1-AS1 levels have been characterized with TNM and Barcelona Clinic Liver Cancer (BCLC) stages [33].

Three different studies including [18,22,29] conducted on a total of 285 non-small cell lung cancer (NSCLC) tissues affirmed up-regulation of NCK1-AS1 compared to paired normal tissues. Kaplan-Meier survival analysis showed that higher expression of NCK1-AS1 is negatively correlated with overall survival of the NSCLC patients [22].

Some of the early inquiries on the role of NCK1-AS1 have been performed on cervical cancer. In the study conducted by Huang L and colleges, NCK1-AS1 has been shown to be up-regulated in both cervical cancer cell lines and tissues. Up-regulation of this lncRNA results in

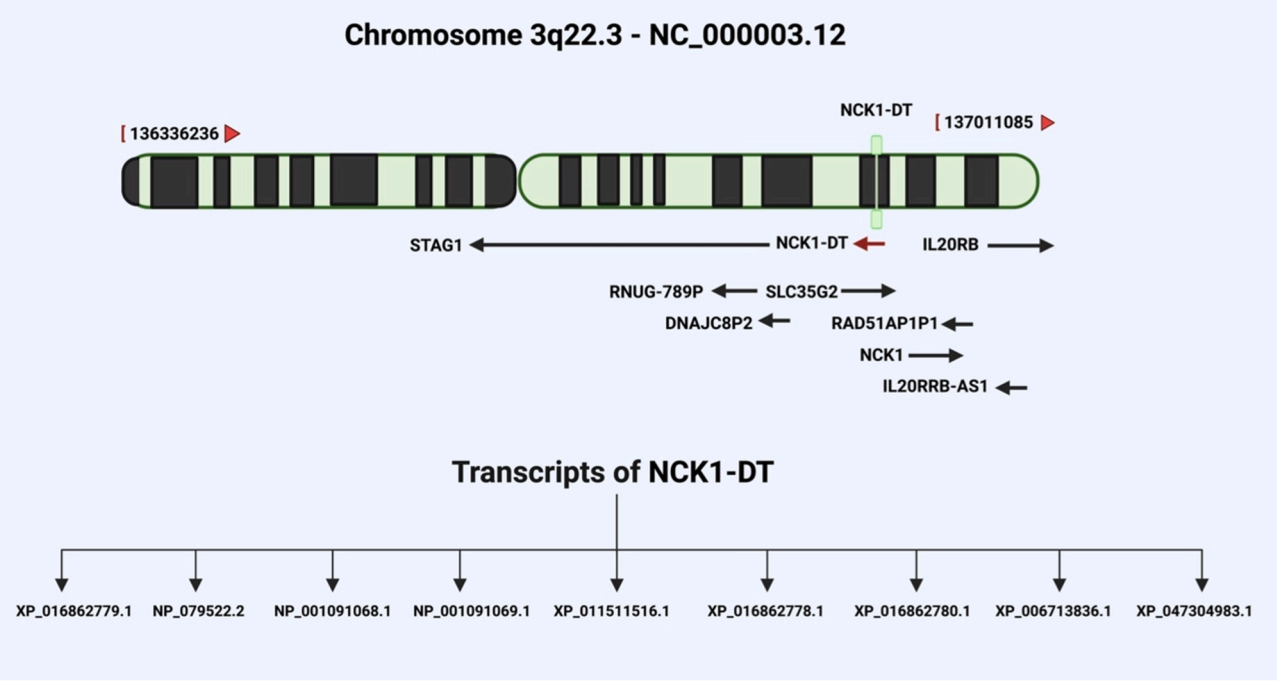

Fig. 1. The location and transcripts of lncRNA NCK1-DT.

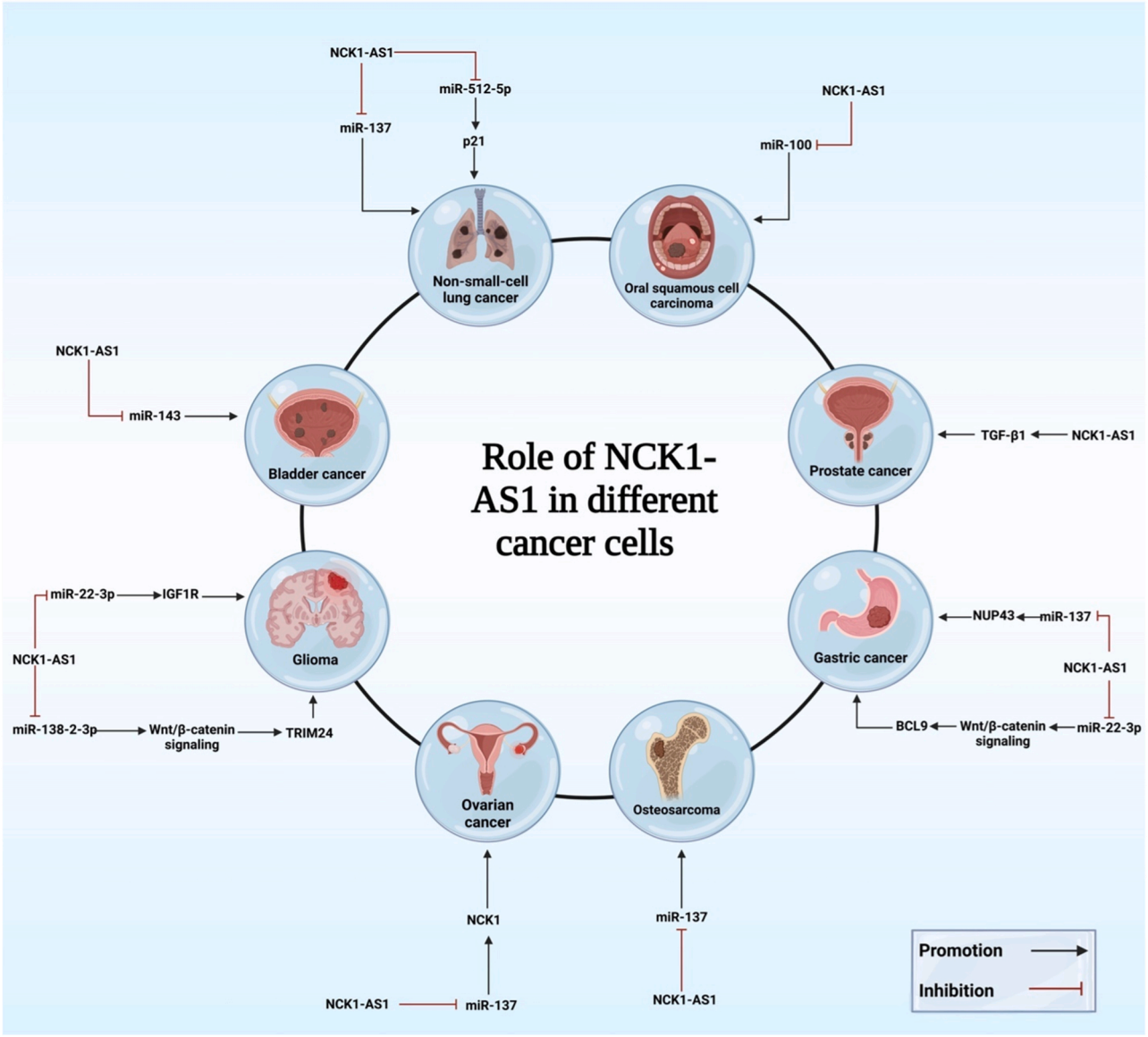

Fig. 2. Various functions of the lncRNA NCK1-AS1 in cancer cells. By directly targeting a certain gene, activating a signaling pathway, or sponging miRNAs, NCK1-AS1 can function as an oncogene.

lowered levels of miR-134 and contributes to malignancy [31]. Furthermore, after dividing patients into high level and low level NCK1-AS1 and evaluating clinicopathologic characteristics, a positive correlation has been confirmed between NCK1-AS1 levels and lymph node metastasis [31].

Cumulatively, NCK1-AS1 is up-regulated in different cancers and is associated with poor prognosis (Table 3).

The diagnostic role of NCK1-AS1 has been assessed in oral squamous cell carcinoma (OSCC) [16], NSCLC [18], prostate cancer [12] and NPC [13] (Table 4). Plasma level of NCK1-AS1 could differentiate patients with OSCC from oral ulcer with AUC value of 0.93 [16]. Moreover, plasma levels of this lncRNA could separate OSCC patients from healthy control with AUC value of 0.88 [16]. Moreover, plasma level of NCK1-AS1 has been found to effectively differentiate between prostate cancer patients and both healthy controls and patients with benign prostate hyperplasia [12]. Plasma levels of NCK1-AS1 have also been shown to be considerably higher in patients with NPC compared with those having temporomandibular joint or healthy persons. Ther has been no significant difference in expression levels of this lncRNA between two latter study subgroups [13].

2.4. Non-malignant conditions

Participation of NCK1-AS1 in non-malignant conditions has been evaluated in atherosclerosis. Expression of NCK1-AS1 has been shown to be increased in blood specimens of patients with atherosclerosis and in ox-LDL induced vascular smooth muscle cells (VSMCs). NCK1-AS1 silencing has enhanced viability of VSMCs, decreased their apoptosis and reduced levels of MDA. Moreover, expressions of proinflammatory cytokines (IL-1β, IL-6 and TNK-α) have been decreased in ox-LDL induced VSMCs after NCK1-AS1 silencing. Functionally, NCK1-AS1 increases expression of COX10 via sponging miR-1197. Besides, simultaneous administration of short hairpin-NCK1-AS1 and miR-1197 antagomir, or co-transfection of short hairpin -NCK1-AS1 and COX10 overexpressing plasmids has caused reduction of cell viability, enhancement of apoptosis, and elevation of MDA levels in VSMCs. Cumulatively, NCK1-AS1 silencing can attenuate development of atherosclerosis through regulation of miR-1197/COX10 axis [30].

Table 1
Role of NCK1-AS1 in cancer cell lines (**Δ**: knock-down or deletion, ↑: over-expression, →: results in, TMZ: temozolomide).

Cancer cell lines	Targets/ Regulators and pathways	Cell line	Function	References
Laryngeal Squamous Cell Carcinoma	miR-137/ NCK1 Axis	-	Δ NCK1-AS1 (which sponges miR-137) → ↑ miR-137 → ↓ NCK1: ↓ proliferation ↓ migration ↓ invasion ↓ viability ↑ apoptosis	[27]
Esophageal squamous cell carcinoma	TGF-β1	EC109 and KYSE150	↑ NCK1-AS1 → ↑ TGF-β1: ↑ migration ↑ invasion	[7]
Nasopharyngeal Carcinoma	miR-135a	C666–1 and 13–9B	Δ NCK1-AS1 → ↑ miR-135a: ↓ migration ↓ invasion	[13]
Hepatocellular carcinoma	miR-22–3p/ YARS, PI3K/AKT pathway	Hep-3B, Huh7, HepG2 and SK-Hep1	Δ NCK1-AS1 (which enriches miR-22–3p) → ↓ YARS → ↓ PI3K/ AKT: ↓ viability ↑ apoptosis ↓ colony formation	[33]
Gastric cancer	miR-22–3p/ BCL9, Wnt/ β-catenin pathway	HGC-27, NCI-N87, MKN-45, and AGS	Δ NCK1-AS1 (which sponges miR-22–3p) → ↑ miR-22–3p → ↓ BCL9 → Wnt/ β-catenin inhibition: ↓ proliferation ↓ migration ↓ invasion ↓ stemness	[11]
	miR-137/ NUP43	BGC-823 and MGC-803	Δ NCK1-AS1 (which sponges miR-137) → ↑ miR-137 → ↓ NUP43: ↓ proliferation ↓ migration ↓ invasion ↓ colony formation	[19]
Melanoma	miR-526b-5p/ ADAM15 axis	A-375, M21, A-875, A2058 and M14	Δ NCK1-AS1 (which sponges miR-526b-5p) → ↑ miR-526b-5p → ↓ ADAM15: ↓ proliferation ↓ migration ↓ colony formation	[21]
Lung squamous cell carcinoma	NCK1/MYC	H2170, H1703, EBC-1, and SK-MES-1	Δ NCK1-AS1 (which interacts with MYC) → ↓ NCK1: ↓ proliferation ↓ migration ↑ apoptosis	[34]
Non-small cell lung Cancer	CDK1	A549, NCI-H1299, PC-9 and NCI-H1650	Δ NCK1-AS1→ ↓ CKD1: ↓ proliferation ↑ cell cycle arrest ↓ colony formation	[29]
	miR-512–5p/p21 axis	H226, A549, H358, H1299 and H520	Δ NCK1-AS1 (which adsorbs miR-512–5p) → ↑ miR-512–5p → ↓ p21: ↓ proliferation ↓ migration ↓ invasion	[22]
	miR-137	A549, SPC-A-1, SK-MES-1, H1299 and 95D	Δ NCK1-AS1 (which sponges miR-137) → ↑ miR-137: ↓ proliferation ↓ migration ↓ invasion	[18]
Prostate cancer	-	PC-3, LNCaP, 22Rv1, DU145	Δ NCK1-AS1: ↓ proliferation ↓ migration ↓ invasion ↑ cell cycle arrest ↑ apoptosis	[20]
	TGF-β1	DU145 and 22Rv1	↑ NCK1-AS1 → ↑ TGF-β1: ↑ migration ↑ invasion	[12]
Oral squamous cell carcinoma	miR-100	SCC090 and SCC25	↑ NCK1-AS1 → increased methylation ↓ miR-100: ↑ migration ↑ invasion	[16]
Glioma	miR-22–3p/ IGF1R axis	A172, LN229, U251 and U87	Δ NCK1-AS1 (which sponges miR-22–3p) → ↑ miR-22–3p → ↓ IGF1R ↓ proliferation ↓ chemoresistance (cisplatin) ↓ radio resistance ↑ apoptosis	[28]
	miR-138–2–3p/ TRIM24 axis, Wnt/ β-catenin	U251, SHG-441, U87 and T98	Δ NCK1-AS1 (which sponges miR-138–2–3p) → ↑ miR-138–2–3p → ↓ TRIM24 → inhibition of Wnt/β-catenin: ↓ proliferation ↓ migration ↓ invasion ↑ cell cycle arrest ↑ apoptosis ↓ stemness	[14]
	miR-137/ TRIM24 axis	U251, A172	Δ NCK1-AS1 → ↑ miR-137 → ↓ TRIM24 ↑ sensitivity to TMZ	[2]
Bladder cancer	miR-143	HT-1376 and HT-1197	↑ NCK1-AS1 → ↓ miR-143: ↑ stemness ↑ proliferation	[24]
Ovarian cancer	miR-137/ NCK1 axis c-Cbl	SNU119, Caov3, SKOV3, OVCAR-3, SUN8	Δ NCK1-AS1 → reduced interaction with c-Cbl + ↑ miR-137 → ↓ NCK1: ↓ proliferation ↓ migration ↓ invasion	[1]

(*continued on next page*)

Table 1 (*continued*)

Cancer cell lines	Targets/ Regulators and pathways	Cell line	Function	References
			↑ apoptosis ↓ resistance to cisplatin	
Osteosarcoma	miR-137	MG63, KHOS and U2OS	Δ NCK1-AS1 → ↑ miR137: ↓ proliferation ↓ migration ↓ invasion ↑ sensitivity to cisplatin	[3]
Cervical cancer	miR-134	SiHa, HeLa, C-33A and CaSki	Δ NCK1-AS1 → ↑ miR-134 ↓ migration ↓ invasion	[31]
	miR-134–5p/ MSH2 axis	HeLa	Δ NCK1-AS1 → ↑ miR-134–5p → ↓ MSH2: ↑ apoptosis ↓ resistance to cisplatin	[32]
	miR-6857/ CDK1, SP1	HeLa, C33A, SiHa and CaSki	Δ NCK1-AS1 (which sponges miR-6857) → ↑ miR-6857 → ↓ CDK1: ↓ proliferation ↓ migration **Note:** SP1 upregulated NCK1-AS1	[17]

3. Discussion

NCK1-AS1 is an lncRNA whose roles in the development of human disorders are being elucidated in recent years. Although dysregulation of this lncRNA has been reported in a variety of malignant conditions, its effects in the etiology on non-malignant conditions are less studied. In fact, atherosclerosis is the only non-malignant disorder in which NCK1-AS1 has an established role.

The main mechanism leading to up-regulation of NCK1-AS1 in cancerous tissues has not been studied ye. However, several studies have found that it serves as a sponge for a range of tumor suppressor miRNAs and reduces their bioavailability. This results in up-regulation of possibly oncogenic targets of these miRNAs. The sponging effects of NCK1-AS1 on miR-137 have been verified in different cancer cell line, including those originated from laryngeal squamous cell carcinoma, gastric cancer, lung cancer, glioma, ovarian cancer and osteosarcoma, suggesting NCK1-AS1/miR-137 axis as a potential therapeutic target for these types of cancers. Moreover, NCK1-AS1 has been shown to regulate activity of miR-22–3p/YARS, miR-22–3p/BCL9, miR-137/NUP43, miR-512–5p/p21, miR-526b-5p/ADAM15, miR-22–3p/IGF1R, miR-138–2–3p/TRIM24, miR-137/TRIM24, miR-134–5p/MSH2 and miR-6857/CDK1 axes. Finally, PI3K/AKT, Wnt/β-catenin and TGF-β pathways are among the most important signaling pathways being regulated by NCK1-AS1.

Most notably, plasma levels of NCK1-AS1 can be used for differentiation of patients suffered from a variety of cancers from healthy controls. This finding has led to suggestion of this lncRNA as a non-invasive marker for patients' follow-up. Typically, over-expression of NCK1-AS1 in tumoral tissues has been associated with poor clinical outcome and higher incidence of tumor metastases, indicating a prognostic role for this lncRNA.

Although both in vitro and in vivo studies have confirmed the efficacy of NCK1-AS1-targeting modalities in reduction of cell proliferation, tumor growth and tumor burden, these modalities have not been used in clinical settings possibly due to safety and bioavailability concerns. Therefore, future studies are needed to evaluate this aspect and find possible mechanisms of dysregulation of this lncRNA in malignant tissues.

Table 2
In vivo studies on the effect of NCK1-AS1 in different mice models (Δ: knock-down or deletion).

Tumor type	Animal models	Results	Pathway	References
Gastric cancer	Nude mice	Δ NCK1-AS1: ↓ tumor growth ↓ tumor volume	Wnt/β-catenin	[11]
		Δ NCK1-AS1: ↓ tumor growth		[19]
Melanoma		Δ NCK1-AS1: ↓ tumor growth ↓ tumor weight	miR-526b-5p/ ADAM15 axis	[21]
Lung squamous cell carcinoma		Δ NCK1-AS1: ↓ tumor growth	NCK1/MYC	[34]
Non-small cell lung Cancer		Δ NCK1-AS1: ↓ tumor growth ↓ tumor weight ↓ tumor volume	-	[18]
Glioma		Δ NCK1-AS1: ↓ tumor growth	miR-22–3p/ IGF1R axis	[28]
		Δ NCK1-AS1: ↓ tumor formation		[14]
Cervical cancer		Δ NCK1-AS1: ↓ tumor weight ↓ tumor volume	miR-6857/ CDK1 axis	[17]

Ethics approval and consent to participant

Not applicable.

Consent of publication

Not applicable.

Authors' contributions

SGF wrote the draft and revised it. MT designed and supervised the study. AK, KBM, BMH and AA collected the data and designed the figures and tables. All the authors read the submitted version and approved it.

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Table 3
Dysregulation of NCK1-AS1 in clinical specimens (ANT: adjacent normal tissue, OS: overall survival, DFS: disease-free survival, GEPIA: Gene Expression Profiling Interactive Analysis, GEO: Gene Expression Omnibus, OU: oral ulcer, FP: first progression, PTBE: peritumoral brain edema, TMJ: temporomandibular joint cases, BPH: benign prostate hyperplasia).

Tumors	Samples	Expression (tumor vs. normal)	Kaplan-Meier Analysis (Impact of NCK1-AS1 dysregulation)	Univariate/ Multivariate cox regression	Association of NCK1-AS1 expression with clinical features	References
Esophageal squamous cell carcinoma (ESCC)	52 ESCC + paired ANT	Upregulated	Shorter OS	-	-	[7]
Hepatocellular carcinoma (HCC)	88 HCC + paired ANT + star base database (374 HCC) + GEPIA	Upregulated	Shorter OS	Independent predictive factor for OS	Associated with TNM stage, BCLC stage and survival status	[33]
Gastric cancer (GC)	36 GC + paired ANT	Upregulated	Shorter OS	-	Associated with lymph node metastasis	[11]
	52 GC + paired ANT	Upregulated	-	-	-	[19]
Lung squamous cell carcinoma (LSCC)	GEPIA + TCGA (486 LSCC + 338 normal tissues)	Upregulated	-	-	-	[34]
Non-small cell lung Cancer (NSCLC)	64 NSCLC + paired ANT	Upregulated	-	-	Associated with tumor size, TNM stage and lymph node metastasis	[29]
	73 NSCLC + paired ANT	Upregulated	Shorter OS/early FP	-	-	[22]
	148 NSCLC + paired ANT	Upregulated	Shorter OS and DFS	Independent prognostic markers in OS and DFS	Associate with TNM stage and lymph node metastasis	[18]
Prostate cancer (PCa)	116 PCa + paired ANT	Upregulated	Shorter OS	-	Associated with TNM stage, Gleason scores and lymph node metastasis	[20]
	Plasma of 60 PCa +58 BPH + 60 healthy controls	Upregulated in PCa				[12]
Oral squamous cell carcinoma (OSCC)	Plasma of 55 OSCC +49 OU +55 healthy controls	Upregulated in OSCC	-	-	-	[16]
Glioma	40 glioma tissues (low-grade: 9 and glioblastoma: 31) + TCGA	Upregulated (especially in glioblastoma)				[28]
	32 glioma tissues +12 normal brain tissues + TCGA (163 tumor tissues + 207 normal tissues) + GSE50161 and GSE35493 datasets +	Upregulated	-	-	-	[14]
	36 fresh glioma tissues + PTBE + recurrent tumor tissues (from same patients)	Upregulated (especially in recurrent tissues)	-	-	-	[2]
Bladder cancer (BCa)	60 BCa + paired ANT	Upregulated	Shorter OS	-	-	[24]
Ovarian cancer	TCGA (426 tumor tissues+ 88 normal tissues)	Upregulated	-	-	-	[1]
Nasopharyngeal Carcinoma (NPC)	Plasma of 50 NPC +50 TMJ +50 healthy controls	Upregulated in NPC	-	-	-	[13]
Cervical cancer (CC)	52 CC + paired ANT	Upregulated	Shorter survival	-	Associated with lymph node metastasis and advanced clinical stage	[31]
	75 CC + paired ANT + GSE63514 and GSE27678 datasets	Upregulated	-	-	-	[32]
	31 CC + paired ANT + TCGA	Upregulated	-	-	Associated with histological type and lymph node status	[17]

Table 4
Diagnostic value of NCK1-AS1 in diseases (ANT: adjacent normal tissue, OU: oral ulcer, TMJ: temporomandibular joint cases, BPH: benign prostate hyperplasia).

Disease type	Samples	Distinguishing ability	AUC	Sensitivity (%)	Specificity (%)	References
Oral squamous cell carcinoma (OSCC)	Plasma of 55 OSCC +49 OU +55 healthy controls	OSCC vs. OU	0.93	-	-	[16]
		OSCC vs. healthy controls	0.88	-	-	[16]
Non-small cell lung Cancer (NSCLC)	148 NSCLC + paired ANT	Tumor vs. normal	0.7674	69.55	81.37	[18]
Prostate cancer (PCa)	Plasma of 60 PCa +58 BPH +60 healthy controls	PCa vs. BPH	0.95	-	-	[12]
		PCa vs. healthy subjects	0.95	-	-	
Nasopharyngeal Carcinoma (NPC)	Plasma of 50 NPC +50 TMJ +50 healthy controls	NPC vs. TMJ	0.96	-	-	[13]
		NPC vs. healthy controls	0.97	-	-	[13]

Declaration of Competing Interest

The authors declare they have no conflict of interest.

Data availability

Not applicable.

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