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Review

The emerging role of NR2F1-AS1 in the tumorigenesis and progression of human cancer

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ABSTRACT

Long noncoding RNAs (lncRNAs) are transcripts of more than 200 nucleotides that lack the ability to encode protein. Convincing studies have indicated that lncRNAs can act as oncogenes or tumor suppressors by regulating gene expression. The novel lncRNA NR2F1-AS1 was recently found to be abnormally expressed in various malignancies, including hepatocellular carcinoma, gastric cancer, colorectal cancer, pancreatic cancer, breast cancer, lung cancer, thyroid cancer, esophageal squamous cell carcinoma, osteosarcoma, and neuroblastoma. NR2F1-AS1 can modify cell proliferation, invasion, migration, apoptosis, the cell cycle, and glycolysis through various mechanisms involving direct or indirect effects on pathways. Furthermore, NR2F1-AS1 may be a potential therapeutic target and prognostic marker in cancer, as it has been related to the clinicopathological characteristics of cancer patients. Here, we summarize and clarify recent research advances regarding the expression, function, molecular mechanisms, and clinical implications of NR2F1-AS1 in multiple malignant tumors.

1. Introduction

Cancer is a major health challenge [1] and the primary obstacle to increasing life expectancy worldwide [2]. The GLOBOCAN 2020 study [3] reported 19.3 million new cases of cancer and nearly 10 million cancer-related deaths in 2020. Cancer is an important cause of morbidity and mortality worldwide at all levels of human development. Although there have been many advances in surgery and chemoradiotherapy in the past few decades, the lack of effective tumor biomarkers hinders the effective application of therapeutic strategies in clinical practice. It is therefore necessary to clarify the potential mechanisms of tumor occurrence and development to improve tumor diagnosis and treatment.

Recent studies have confirmed that long noncoding RNAs (lncRNAs) are major regulators in human tumors. LncRNAs are conserved and polyadenylated ncRNAs of more than 200 nucleotides that lack the ability to encode proteins [4–6]. LncRNAs are widely found in human tissues and play key roles in multiple physiological and pathological processes, such as transcription, posttranscriptional regulation and

Abbreviations: lncRNAs, long noncoding RNAs; NR2F1-AS1, NR2F1 antisense RNA 1; HCC, hepatocellular carcinoma; GC, gastric cancer; ESCC, esophageal squamous cell carcinoma; PDAC, pancreatic ductal adenocarcinoma; BC, breast cancer; CRC, colorectal cancer; CSCC, cervical squamous cell carcinoma; EC, endometrial cancer; NSCLC, non-small cell lung cancer; TC, thyroid cancer; O-S, osteosarcoma; NB, neuroblastoma; EMT, epithelial–mesenchymal transition; HUVECs, human umbilical vein endothelial cells; TCM, tumor-conditioned medium; MVD, microvessel density; ceRNA, competing endogenous RNA; OS, overall survival; DFS, disease-free survival; BIRC5, baculoviral inhibitor of apoptosis repeat-containing 5; IGF-1, insulin-like growth factor-1; IGF-1R, IGF-1 receptor; ERK, extracellular signal-regulated kinase; FOXA1, forkhead Box A1; ER, estrogen receptor; PR, progesterone receptor; CA19-9, carbohydrate antigen 19-9; AUC, area under the curve; ROC, receiver operating characteristic.

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epigenetic modification [7,8]. Depending on the interactions with specific entities (RNA, DNA, proteins, and signaling pathways), dysregulated lncRNAs can affect cell proliferation, invasion, and metastasis during tumor development. As lncRNAs can be easily targeted therapeutically with high specificity, individualized treatments have been exploited in multiple cancers [9]. LncRNAs are also characterized by their high efficiency, specificity, and stability in tissues and can be used as biomarkers for diagnosis, prognosis, or treatment [10,11].

NR2F1-AS1 (NR2F1 antisense RNA 1) is a gene that encodes a lncRNA. The NCBI database (https://www.ncbi.nlm.nih.gov/) shows that the NR2F1-AS1 gene is located on chromosome 5 (q15 antisense chain), and its gene sequence can be transcribed to 10 transcripts: NR_109823.1, NR_109820.1, NR_109824.1, NR_021491.2, NR_109821.1, NR_109822.1, NR_109825.1, NR_021490.2, NR_109818.1, and NR_109819.1 (Fig. 1).

In addition, NR2F1-AS1 is expressed in multiple normal human tissues (brain, heart, liver, ovary, and thyroid) and can be found in the GeneCards database (https://www.genecards.org/). NR2F1-AS1 is mainly localized in the nucleus and cytoplasm (Table 1) according to the lncLocator database (http://www.csbio.sjtu.edu.cn/bioinf/lncLocator/).

Huang and colleagues [12] reported that NR2F1-AS1 regulates oxaliplatin resistance by targeting ABCC1 via miR-363 in hepatocellular carcinoma (HCC). Their study was the first to explore the role of NR2F1-AS1 in cancer. A subsequent study [13] found that HCC patients with increased NR2F1-AS1 had poor overall survival (OS). Our research team was interested in the role of NR2F1-AS1 in the development of pancreatic ductal adenocarcinoma (PDAC) and found that increased expression of NR2F1-AS1 promoted the progression of PDAC and was associated with poor prognosis. Accumulating evidence has shown that NR2F1-AS1 participates in the regulation of proliferation, migration, and invasion in multiple types of tumors.

We summarize the current understanding of the dysregulated expression, functions, and regulatory mechanisms (Table 2) as well as the clinical significance (Table 3) of NR2F1-AS1 and explore its potential applications in the clinical treatment of tumors.

2. Role of NR2F1-AS1 in cancer

2.1. Role of NR2F1-AS1 in digestive tract tumors

2.1.1. Hepatocellular carcinoma (HCC)

Huang et al. [12] first reported that NR2F1-AS1 regulates oxaliplatin resistance in HCC by targeting ABCC1 via miR-363. RT–PCR analysis showed that NR2F1-AS1 levels were increased in oxaliplatin-resistant HCC. Moreover, NR2F1-AS1 silencing reduced the expression of genes related to invasion, migration, and drug resistance and reduced IC50 values in resistant cells; this result was further confirmed in a xenograft nude mouse model. This study concluded that NR2F1-AS1 regulates OXA resistance in HCC by targeting the miR-363–ABCC1 pathway. Li et al. [13] found that HCC patients with increased NR2F1-AS1 had poor OS. NR2F1-AS1 knockdown inhibited hypoxia-induced glycolysis and migration in HCC cells by upregulating miR-140 and inhibiting HK2. Wen et al. [14] showed that increased NR2F1-AS1 expression was related to advanced stage HCC. Inhibition of NR2F1-AS1 promoted apoptosis and suppressed epithelial–mesenchymal transition (EMT). NR2F1-AS1 promoted cell invasion and migration, which positively regulated DEK expression by suppressing miR-642a in HCC [15]. These studies suggested that NR2F1-AS1 is an oncogene in HCC and plays a crucial role in tumor initiation and development. Therefore, NR2F1-AS1 might be a novel target for the diagnosis and treatment of HCC.

Table 1
Analysis of the subcellular localization of NR2F1-AS1 from lncLocator database.

Subcellular locations	Score
Cytoplasm	0.604346301765
Nucleus	0.219035823364
Ribosome	0.0134009637433
Cytosol	0.0493574701446
Eosome	0.113859440983

2.1.2. Gastric cancer (GC)

A study by Liao et al. [16] showed that NR2F1-AS1 was upregulated in GC. NR2F1-AS1 silencing significantly suppressed GC cell proliferation and migration and enhanced cell apoptosis. In addition, NR2F1-AS1 sponged miR-493-5p. MAP3K2 is a downstream gene of miR-493-5p, and NR2F1-AS1 counteracted the inhibition of miR-493-5p. Lv's study [17] confirmed that NR2F1-AS1 regulates the miR-190a/PHLDB2 pathway and affects EMT. Another study [18] showed that NR2F1-AS1 might enhance GC cell proliferation, invasion, and migration by recruiting SPI1, which increased the expression of ST8SIA1.

2.1.3. Colorectal cancer (CRC)

Wang et al. [19] reported that NR2F1-AS1 expression was decreased in CRC and was associated with poor patient survival. NR2F1-AS1 upregulated TOB1 (a target of miR-371a-3p) by directly interacting with miR-371a-3p. NR2F1-AS1 and TOB1 overexpression reduced the proliferation of CRC cells, suggesting that NR2F1-AS1 suppresses CRC cell proliferation by regulating the miR-371a-3p/TOB1 axis.

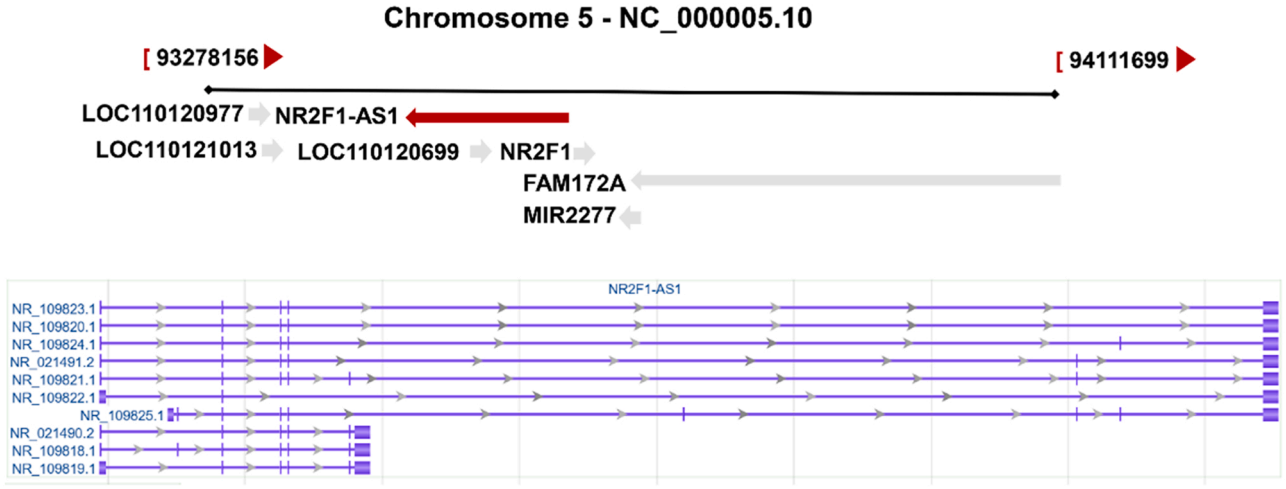

Fig. 1. Schematic diagram of the formation of lncRNA NR2F1-AS1.

Table 2
Functional characterization of the lncRNA NR2F1-AS1 in various cancers.

Type of cancer	Expression	Functions	Related genes	Role	Reference
Hepatocellular carcinoma	Upregulated	Proliferation, migration, invasion, apoptosis, EMT, drug resistance, glycolysis	miR-363, ABCC1, miR-140, HK2, miR-642a, DEK	oncogene	[12–15]
Gastric cancer	Upregulated	Proliferation, migration, apoptosis, EMT	MAP3K2, miR-493-5p, PHLDB2, miR-190a, AKT3, ST8SIA1, SPI1	oncogene	[16–18]
Colorectal cancer	Downregulated	Proliferation	TOB1, miR-371a-3p	tumor suppressor	[19]
Pancreatic ductal adenocarcinoma	Upregulated	Proliferation, invasion, migration, cell cycle	miR-146a-5p, miR-877-5p, GALNT10, ZNF532, SLC39A1, PGK1, LCO3A1, NRP2, LPCAT2, PSMA4, CLTC	oncogene	[20]
Esophageal squamous cell carcinoma	Upregulated	Proliferation, invasion, migration, metastasis, EMT	EMT molecular markers, GLI2	oncogene	[21,23]
Breast cancer	Upregulated	Proliferation, invasion, migration, metastasis	IGF-1R, CD31, CD34, ER, PR, HER2	oncogene	[24,25]
Cervical squamous cell carcinoma	Downregulated	Invasion, migration	SIK1, miR-17	tumor suppressor	[26]
Endometrial cancer	Upregulated	Proliferation, migration, invasion, apoptosis	SOX4, miR-363	oncogene	[27]
Non-small cell lung cancer	Upregulated	Proliferation, migration, invasion, apoptosis	ITGB1, miR-493-5p	oncogene	[28]
Thyroid cancer	Upregulated	Proliferation, migration, apoptosis	CCND1, miR-338-3p; SOX12, miR-423-5p	oncogene	[29,30]
Osteosarcoma	Upregulated	Proliferation, migration, invasion, cell cycle, apoptosis	BIRC5, miR-485-5p/miR-218-5p, FOXA1, miR-483-3p	oncogene	[31,32]
Neuroblastoma	Upregulated	Proliferation, migration, invasion, apoptosis	TRIM2, miR-493	oncogene	[33]

Table 3
Clinical significance of NR2F1-AS1 in various tumors.

Cancer	Relationships with clinical features	Reference
Hepatocellular carcinoma	Advanced TNM stage, poor survival, AUC > 0.8.	[13–15]
Gastric cancer	Pathological features, staging, poor prognosis, and EMT process	[16,17]
Colorectal cancer	Poor overall survival(OS)	[19]
Pancreatic ductal adenocarcinoma	Poor OS and disease free survival	[20]
Esophageal squamous cell carcinoma	Unknown	[21,23]
Breast cancer	Recurrence	[25]
Cervical squamous sell carcinoma	In clinical stages	[26]
Endometrial cancer	Unknown	[27]
Non small cell lung cancer	Tumor size, TNM stage, lymph node metastasis , poor OS	[28]
Thyroid cancer	Unknown	[29,30]
Osteosarcoma	Clinical stage and distant metastasis, OS	[31,32]
Neuroblastoma	Poor OS	[33]

2.1.4. Pancreatic ductal adenocarcinoma (PDAC)

Luo's study [20] found that NR2F1-AS1 was highly expressed in PDAC and was associated with poor OS and disease-free survival (DFS). NR2F1-AS1 knockdown suppressed cell proliferation, migration, and invasion in vitro and tumorigenesis in vivo. By sponging miR-146a-5p and miR-877-5p, NR2F1-AS1 regulated 10 key genes and downstream targets of these miRNAs, such as GALNT10, ZNF532, SLC39A1, PGK1, LCO3A1, NRP2, LPCAT2, PSMA4, and CLTC. These findings suggested that NR2F1-AS1 functions as a competing endogenous RNA (ceRNA) in PDAC pathogenesis by competitively binding miR-146a-5p and miR-877-5p.

2.1.5. Esophageal squamous cell carcinoma (ESCC)

Zhang et al. [21] showed that NR2F1-AS1 levels were elevated in ESCC cells. NR2F1-AS1 knockdown decreased the expression of GLI2, a key protein involved in the Hedgehog signaling pathway in ESCC. This finding suggested that NR2F1-AS1 can promote ESCC progression by activating the Hedgehog signaling pathway. In addition, NR2F1 activated NR2F1-AS1 transcription in ESCC. A recent cancer study identified NR2F1 as an important transcription factor [22]. Briefly, NR2F1-induced NR2F1-AS1 facilitates ESCC progression by activating the Hedgehog signaling pathway. P. Ren et al. [23] revealed that increased expression of NR2F1-AS1 enhanced tumor cell proliferation and metastasis in ESCC by regulating EMT markers.

2.2. Role of NR2F1-AS1 in gynecological oncology

2.2.1. Breast cancer (BC)

Zhang et al. [24] found that NR2F1-AS1 was positively correlated with CD31 and CD34 in BC and facilitated tube formation by human umbilical vein endothelial cells (HUVECs). NR2F1-AS1 promoted HUVEC proliferation, tube formation, and migration in tumor-conditioned medium (TCM). In a zebrafish model, NR2F1-AS1 augmented cell-related neovasculature and subsequently facilitated metastasis in BC. In a mouse model, NR2F1-AS1 increased tumor vessel formation, microvessel density (MVD) and promoted primary tumor growth. Another study [25] reported that NR2F1-AS1 was related to carcinoma recurrence and regulated by the progesterone receptor (PR)/estrogen receptor (ER) transcriptional complex. In addition, NR2F1-AS1 induced a quiescent-like state in ER-positive BC cells.

2.2.2. Cervical squamous cell carcinoma (CSCC)

The study by Peng et al. [26] showed that NR2F1-AS1 was downregulated in CSCC. Decreased NR2F1-AS1 was associated with advanced clinical stage disease. NR2F1-AS1 can upregulate SIK1, a target of miR-17, by directly interacting with miR-17. Increased expression of NR2F1-AS1 and SIK1 reduced CSCC cell invasion and migration. Upregulation of miR-17 had the opposite results and alleviated the effects of NR2F1-AS1 and SIK1. Therefore, NR2F1-AS1 may suppress tumor cell invasion and migration through the miR-17/SIK1 axis in CSCC.

2.2.3. Endometrial cancer (EC)

Wang et al. [27] found that NR2F1-AS1 expression was increased in EC. Silencing NR2F1-AS1 reduced EC cell viability, migration, and invasion and enhanced cell apoptosis. miR-363 was negatively correlated with NR2F1-AS1, and SOX4 was identified as a target of miR-363. NR2F1-AS1 also participated in EC development by activating the PI3K/AKT/GSK-3β pathway.

2.3. Role of NR2F1-AS1 in other tumors

2.3.1. Non-small cell lung cancer (NSCLC)

A study by Zhang et al. [28] showed that increased NR2F1-AS1 was correlated with adverse clinical characteristics and poor OS in NSCLC patients. Silencing NR2F1-AS1 alleviated NSCLC cell proliferation, migration, and invasion and promoted tumor cell apoptosis. In addition, NR2F1-AS1 silencing suppressed tumor growth by NSCLC cells in an in vivo model. Mechanistically, NR2F1-AS1 increased ITGB1 expression by sponging miR-493-5p. These data indicated that the NR2F1-AS1/miR-493-5p/ITGB1 pathway is involved in promoting NSCLC progression.

2.3.2. Thyroid cancer (TC)

Guo et al. found that NR2F1–AS1 expression was increased in TC, and NR2F1–AS1 silencing inhibited TC cell proliferation and migration but promoted cell apoptosis [29]. Another study [30] found that NR2F1–AS1 promoted TC cell proliferation and invasion by interacting with miR-423-5p and then upregulating SOX12 expression. These findings indicated NR2F1–AS1 as a potential therapeutic target in TC.

2.3.3. Osteosarcoma (O-S)

Li et al. [31] showed that NR2F1-AS1 expression was increased in O-S and was correlated with distant metastasis, advanced stage, and shorter OS in O-S patients. Silencing NR2F1-AS1 suppressed cell proliferation, migration, and invasion; arrested the cell cycle; promoted apoptosis in vitro; and decreased tumor growth in vivo. NR2F1-AS1 upregulated forkhead box A1 (FOXA1) expression by directly sponging miR-483-3p. Another study [32] revealed that NR2F1-AS1 targeted miR-485-5p and miR-218-5p, both of which directly target baculoviral inhibitor of apoptosis repeat-containing 5 (BIRC5) in O-S. Additionally, by regulating BIRC5, NR2F1-AS1 affected O-S cell proliferation, migration, invasion, and apoptosis. Specifically, silencing NR2F1-AS1 suppressed the malignant phenotype by affecting the interacts with miR-485-5p and miR-218-5p and the downregulation of BIRC5 in O-S cells. These findings suggested that the NR2F1-AS1/miR-485-5p/miR-218-5p/BIRC5 axis is a potential target for O-S treatment.

2.3.4. Neuroblastoma (NB)

Liu et al. [33] showed that high expression of NR2F1-AS1 was associated with poor prognosis in NB. Silencing NR2F1-AS1 inhibited NB cell proliferation, migration, and invasion and promoted apoptosis. MiR-493 was identified as a downstream target of NR2F1-AS1, and TRIM2 was directly targeted by miR-493 in NB. Mechanistically, NR2F1-AS1 promoted NB progression by sponging miR-493 to regulate TRIM2.

NR2F1-AS1 mainly regulates the development and progression of tumors by regulating tumor cell proliferation, migration, invasion, and apoptosis. NR2F1-AS1 is upregulated in most tumors and acts mainly as an oncogene. However, it is downregulated in a few types of cancer (e.g., CRC and CSCC), suggesting tumor suppressor function. To date, only Huang et al. have shown that NR2F1-AS1 can regulate oxaliplatin resistance in HCC; such activity has not been reported in other tumors. This may represent an opportunity for further study in the future.

3. Mechanisms of NR2F1-AS1 in cancer

The mechanisms by which NR2F1-AS1 is involved in cancer can be summarized into four categories: ceRNA function, direct interactions with mRNA, protein interactions, and pathway interactions (Fig. 2).

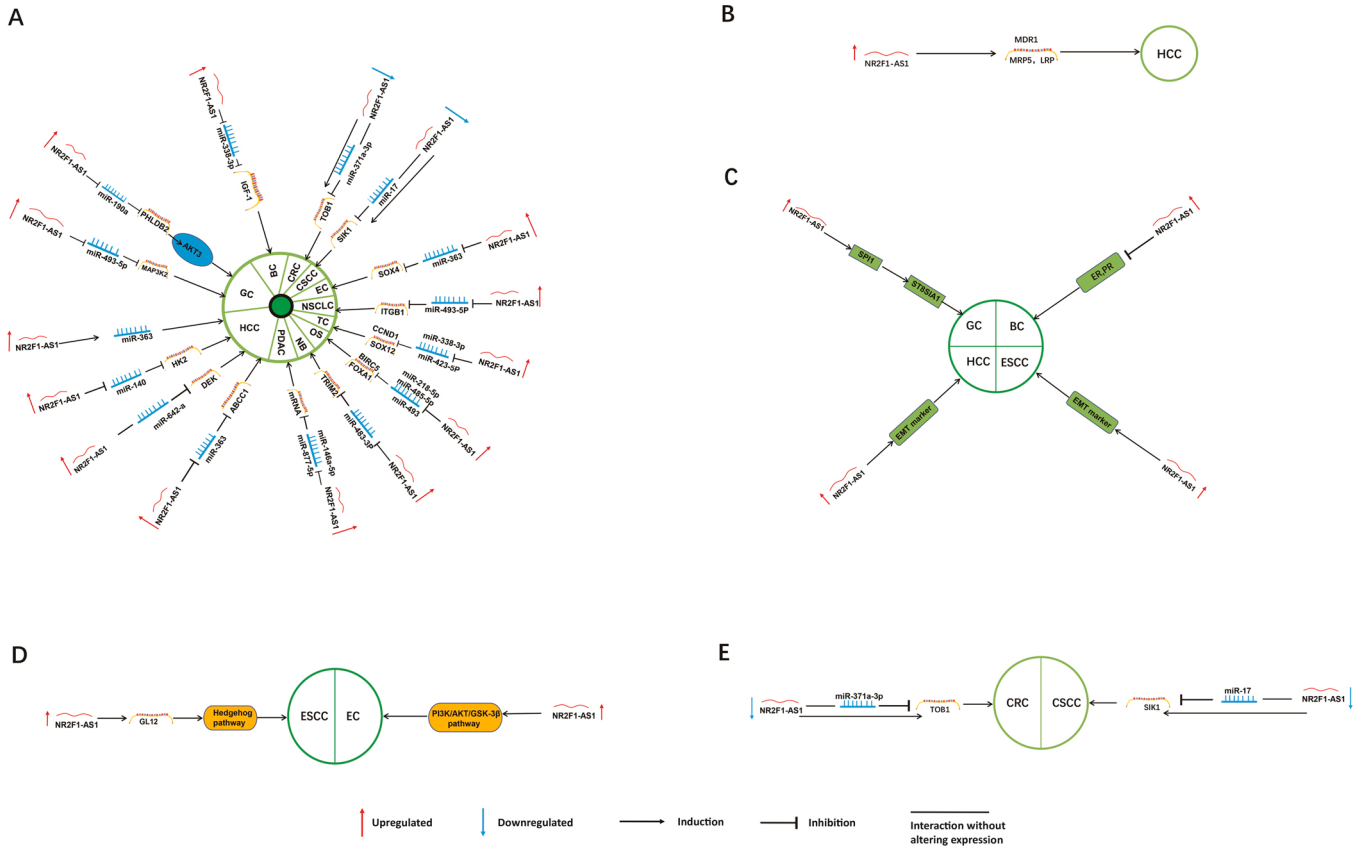

Fig. 2. NR2F1-AS1 mediates mechanisms involved in cancer progression. (A) NR2F1-AS1 functions as a ceRNA. (B) NR2F1-AS1 directly interacts with mRNAs. (C) NR2F1-AS1 interacts with protein. (D-E) NR2F1-AS1 interacts with pathway.

3.1. NR2F1-AS1 functions as a ceRNA

Previous studies have indicated that NR2F1-AS1 mainly functions as a sponge to competitively bind miRNA (ceRNA mechanism) and thereby regulate downstream mRNA expression. A group at Harvard Medical School recently proposed that ceRNAs regulate gene expression[34]. This study clarified that these RNA transcripts act as endogenous miRNA sponges. Moreover, miRNAs are important negative regulators of mRNA expression in the ceRNA network. Therefore, by competitively binding miRNAs that target mRNAs, lncRNAs act as molecular sponges to regulate the levels of mRNAs [35–37], which undergo demethylation and destabilization. This hypothesis was confirmed by later studies [38–40]. For example, increasing evidence from recent studies shows that lncRNAs may be involved in posttranscriptional regulation by the classic ceRNA mechanism in PDAC [41–43].

HCC: Hepatocellular carcinoma; GC: Gastric cancer; ESCC: Esophageal squamous cell carcinoma; PDAC: Pancreatic ductal adenocarcinoma; BC: Breast cancer; CRC: Colorectal cancer; CSCC: Cervical squamous cell carcinoma; EC: Endometrial cancer; NSCLC: Non-small cell lung cancer; TC: Thyroid cancer; O-S: Osteosarcoma; NB: Neuroblastoma.

NR2F1-AS1 functions as a ceRNA in cancers (Fig. 2A). In oxaliplatin-resistant HCC cells, NR2F1-AS1 was negatively correlated with miR-363, suggesting that ABCC1 has an antagonistic function and is the downstream target of miR-363. Therefore, NR2F1-AS1 regulates ABCC1 protein by sponging miR-363 to promote oxaliplatin resistance in HCC [12]. In addition, NR2F1-AS1 can promote hypoxia-induced glycolysis and migration by facilitating HK2 expression through direct interaction with miR-140 in HCC [13]. GC cell proliferation, migration, and apoptosis can be regulated by NR2F1-AS1, which upregulates MAP3K2 by sponging miR-493-5p [16]. In PDAC, NR2F1-AS1 functions as an oncogene through the ceRNA network by sponging miR-146a-5p and miR-877-5p to promote the expression of downstream target genes that enhance cellular activities, such as proliferation, invasion, migration and the cell cycle [20]. In BC, NR2F1-AS1 acts as a sponge for miR-338-3p to enhance insulin-like growth factor-1 (IGF-1) expression and then activate the IGF-1 receptor (IGF-1R) and extracellular signal-regulated kinase (ERK) pathways [24]. NR2F1-AS1 is involved in EC cell proliferation and migration through the inhibition of miR-363, which targets SOX4 [27]. NR2F1-AS1 functions as an oncogene in NSCLC progression by acting as a ceRNA; it sponges miR-493-5p and targets ITGB1 [28]. NR2F1–AS1 promotes TC progression by sponging miRNA-338-3p to increase CCND1 expression [29]. NR2F1–AS1 also interacts with miR-423-5p to promote SOX12 expression in TC [30]. NR2F1-AS1 enhances the proliferation, migration, invasion, and apoptosis of O-S cells. Silencing NR2F1-AS1 suppresses the malignant phenotype of O-S cells by binding miR-485-5p and miR-218-5p and repressing BIRC5, a member of the inhibitor of apoptosis (IAP) family associated with tumor cell apoptosis [32]. Additionally, NR2F1-AS1 functions as an oncogene by sponging miR-483-3p and promoting its target oncogene FOXA1 in O-S [31]. Through the miR-493/TRIM2 axis, NR2F1-AS1 enhances NB cell progression [33].

3.2. Direct interactions with mRNAs

The mRNA expression of drug resistance-related genes in oxaliplatin-resistant HCC cells, such as MDR1, MRP5, and LRP, can be suppressed by NR2F1-AS1 silencing (Fig. 2B), suggesting that NR2F1-AS1 knockdown can inhibit oxaliplatin resistance [12].

3.3. Protein interactions

NR2F1-AS1 may enhance GC cell proliferation, invasion, and migration by recruiting SPI1 to promote the expression of ST8SIA1 [18]. NR2F1-AS1 is involved in tumor recurrence in BC, and its expression level is mediated by the ER/PR transcriptional complex [25]. NR2F1-AS1 can promote EMT in HCC cells by regulating EMT markers (including E-cadherin, N-cadherin, SNAIL, slug, and vimentin) [14]. Western blot analysis indicated that the expression of E-cadherin, N-cadherin, and vimentin was significantly altered after interference with NR2F1-AS1 expression [23] (Fig. 2C).

3.4. Pathway interactions

NR2F1-AS1 promotes ESCC progression by activating the Hedgehog signaling pathway [21]. NR2F1-AS1 modulates EC cell proliferation and migration by regulating the PI3K/AKT/GSK-3β pathway [21] (Fig. 2D). In CRC, NR2F1-AS1 interacts with miR-371a-3p, but the overexpression of each component had no impact on the expression of the other (Fig. 2E). However, increased NR2F1-AS1 levels can lead to the overexpression of TOB1, a target of miR-371a-3p. Therefore, NR2F1-AS1 may suppress the proliferation of CRC cells by regulating the miR-371a-3p/TOB1 axis [19]. Similarly, NR2F1-AS1 also interacts with miR-17 in CSCC [26], but this interaction has no significant effect on the expression of NR2F1-AS1 or miR-17. Interestingly, increased NR2F1-AS1 levels can lead to the overexpression of SIK1, a target of miR-17, suggesting that NR2F1-AS1 suppresses invasion and migration by modulating the miR-17/SIK1 axis in CSCC cells.

The ceRNA mechanism is the predominant regulatory mechanism by which NR2F1-AS1 regulates tumor progression. Firstly, in most tumors, NR2F1-AS1 regulates tumorigenesis through a ceRNA mechanism involving the negative regulation of targeted miRNAs, which consequently regulates downstream targets and pathways. Secondly, NR2F1-AS1 can directly interact with mRNAs and proteins. Then, NR2F1-AS1 can directly (e.g., the PI3K/AKT/GSK-3β pathway) or indirectly (e.g., the Hedgehog signaling pathway) interact with pathways to regulate tumor progression. Finally, NR2F1-AS1 regulates tumor development through an unusual regulatory pathway. In brief, NR2F1-AS1 was shown to be downregulated in CRC and to interact with miR-371a-3p, but the overexpression of these components had no impact on each other. However, increased NR2F1-AS1 levels can lead to the overexpression of TOB1, a target of miR-371a-3p. NR2F1-AS1 regulates tumor development by different mechanisms in different types of cancer, but the ceRNA mechanism is most common. In future studies, we can further explore therapeutic targets or potential regulatory ceRNA mechanisms and then translate the findings into clinical applications.

4. Clinical significance of NR2F1-AS1

4.1. As a diagnostic biomarker in cancer

Early detection is important for improving cancer prognosis. For example, carbohydrate antigen 19-9 (CA19-9) is currently the gold-standard biomarker for pancreatic cancer (PC) [44–46]. However, a previous study showed that the AUC of CA19-9 in diagnosing PC ranged from 0.881 to 0.90 [47,48]. Approximately 5–10% of PC patients are Lewis antigen-negative with little to no secretion of CA19-9. This represents a major limitation of CA19-9 as a diagnostic biomarker [49], rendering it inappropriate for use alone in the early detection of PC. Therefore, new diagnostic markers that are highly specific and sensitive are needed. The serum levels of NR2F1-AS1 are significantly increased in HCC patients, and the AUC of NR2F1-AS1 in the receiver operating characteristic (ROC) curve analysis was greater than 0.8 [14]. The diagnostic value of biomarkers is determined by the ROC curve. The accuracy is considered moderate or high if the AUC is above 0.70 [50]. NR2F1-AS1 may be a potential diagnostic marker in cancer.

4.2. As a biomarker for cancer prognosis

The aberrant expression of NR2F1-AS1 is correlated with prognosis in multiple types of cancer (Table 3). Increased expression of NR2F1-AS1 is related to tumor recurrence in BC [25]. Decreased NR2F1-AS1

expression is correlated with advanced clinical stage disease in CSCC [26]. Elevated NR2F1-AS1 expression is related to tumor size, lymph node metastasis and TNM stage in NSCLC [28]. The overexpression of NR2F1-AS1 is related to clinically advanced stage and distant metastasis in O-S patients [31,32]. Several studies have shown that NR2F1-AS1 may be a prognostic biomarker in patients with HCC [13], GC [16, 17], CRC [19], PC [20], O-S [31] and NB [33].

4.3. As a therapeutic target in cancer

Recent research on NR2F1-AS1 in cancer has explored the potential of NR2F1-AS1 as a therapeutic target (Table 2). In HCC, silencing NR2F1-AS1 suppressed invasion, migration, and drug resistance; reduced IC50 values in vitro and reduced tumor weight in vivo [12,15]; and inhibited glycolysis in vitro [13]. NR2F1-AS1 also promoted apoptosis and inhibited EMT in HCC [14]. Silencing NR2F1-AS1 significantly decreased GC cell proliferation and migration and promoted cell apoptosis [16,18]. Increased expression of NR2F1-AS1 reduced the proliferation rate of CRC cells [19]. Knockdown of NR2F1-AS1 markedly inhibited PC cell proliferation, migration, and invasion; induced cell cycle arrest in vitro; and inhibited tumor growth in vivo [20]. Silencing NR2F1-AS1 reduced the proliferation, migration, and invasion of ESCC cells and restrained EMT and stemness properties by downregulating SHH, GLI2, and GLI1, which are related to the Hedgehog signaling pathway [21]. NR2F1-AS1 silencing suppressed O-S cell proliferation, invasion, and migration and promoted apoptosis [32]. Accumulating in vitro research has confirmed that NR2F1-AS1 inhibition can suppress the progression of BC [24,25], CSCC [26], NSCLC [28], TC [29,30], and NB [33]. Therefore, NR2F1-AS1 is a potential therapeutic target in cancer.

NR2F1-AS1 seems to have potential diagnostic value, but it has only been studied in HCC patients at one institute, and the sample size was small. No relevant studies have yet been reported in other types of cancer. This is a research direction worthy of further study, and studies with a large sample size and multicenter studies are required for further confirmation. NR2F1-AS1 has potential value as a prognostic marker and therapeutic target in a variety of tumors, and further translational research is needed, for example, based on these targets and pathways, to study drug resistance and to develop new drugs. We believe that the clinical value of NR2F1-AS1 will be realized in future clinical work.

5. Summary and outlook

LncRNAs are crucial regulators of tumor initiation and progression. The molecular function of NR2F1-AS1 is associated with the type of tumor. The majority of studies suggest that NR2F1-AS1 is an oncogenic lncRNA that is upregulated in most cancers, and it is mainly involved in cell proliferation, migration, invasion, and apoptosis through the most common ceRNA mechanism or by directly or indirectly interacting with mRNAs, proteins and pathways. Interestingly, in a few types of cancer (such as CRC and CSCC), NR2F1-AS1 is downregulated and functions as a tumor suppressor, decreasing proliferation, migration, and invasion. In terms of clinical potential, aberrant expression of NR2F1-AS1 is associated with clinicopathological characteristics, such as tumor size, TNM stage, EMT, metastasis, recurrence, and OS. Thus, NR2F1-AS1 is a potential prognostic marker and therapeutic target in cancer. However, the diagnostic value remains limited because of limited sample sizes and research on only a few types of cancer. The role of NR2F1-AS1 in drug resistance has not yet been studied in cancer. Research on NR2F1-AS1 in cancer is still in the early stage, and considerable translational research remains to be performed.

NR2F1-AS1 regulates tumor development by different mechanisms in different types of cancer, but the ceRNA mechanism is the most common. In future research, we can explore further therapeutic targets or potential regulatory mechanisms based on the ceRNA mechanism and then translate the findings into clinical applications. Additionally, research on drug resistance, as well as new drug development based on the potential therapeutic targets and mechanisms, will yield new opportunities for cancer treatment.

This review highlights the role and regulatory mechanism of NR2F1-AS1 in multiple types of cancer and presents its clinical implications, expanding our understanding of cancer pathogenesis and providing new insights into the development of novel biomarkers and individualized cancer therapy. NR2F1-AS1 is ultimately expected to have clinical applications in cancer treatment.

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CRediT authorship contribution statement

Dong Luo, LianDong Ji, Xiao Yu: Conceptualization, Data curation. **Dong Luo, Yunfei Liu and Zhiqiang Li**: Analysis and interpretation of the data. **Dong Luo, Yongchao Yang and Hongwei Zhu**: Formal analysis. **Dong Luo**: Project administration. **Dong Luo, Yunfei Liu and Zhiqiang Li**: Investigation, Methodology. **Dong Luo, Yunfei Liu, Xianyun Bi and Shuai Yuan**: Visualization, Investigation. **Dong Luo, Yunfei Liu, Shuai Yuan and Xianyun Bi**: Software. **LianDong Ji and Xiao Yu**: Supervision, Validation. **Dong Luo**: Writing – original draft. **Dong Luo, LianDong Ji and Xiao Yu**: Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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