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Original Article

DANCR: an emerging therapeutic target for cancer

Yuheng Yan[1,2*], Qingmiao Shi[3*], Xin Yuan[3*], Chen Xue[3], Shen Shen[3], Yuting He[1,2]

[1]Key Laboratory of Hepatobiliary and Pancreatic Surgery and Digestive Organ Transplantation of Henan Province, The First Affiliated Hospital of Zhengzhou University, Zhengzhou 450052, Henan, P.R. China; Departments of [2]Hepatobiliary and Pancreatic Surgery, [3]Infectious Diseases, The First Affiliated Hospital of Zhengzhou University, Zhengzhou 450052, Henan, P.R. China. [*]Equal contributors.

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Abstract: The discovery of long non-coding RNAs (lncRNAs) revolutionized the current framework for understanding the molecular mechanisms of tumorigenesis and stimulated the search for targeted cancer treatments. Among lncRNAs, differentiation antagonizing non-protein-coding RNA (DANCR) is a newly identified oncogenic gene that is upregulated in diverse cancer types and has a critical role in cancer progression. Herein, we summarize current knowledge regarding DANCR regulatory functions related to cancer cell proliferation, invasion, metastasis, and chemo-resistance. We also synthesize the effects of DANCR on cancer stemness features, the epithelial-mesenchymal transition (EMT), and angiogenesis, which are essential for the progression of malignant cancer cells. Mechanically, the interaction between DANCR and its targets including microRNAs (miRNAs), mRNAs, and proteins are also elucidated. Finally, we propose DANCR-based therapeutic approaches to provide novel insights about cancer treatment.

Keywords: DANCR, long non-coding RNA, cancer, lncRNA function, mechanism, cancer therapy

Introduction

In the mammalian genome, less than 2% of DNA transcripts have stable protein-coding functions. Instead, most DNA transcripts are non-coding RNAs (ncRNAs), which until recently, had been considered "evolutionary junk" or "transcription noise" [1]. However, with the development of high-throughput technologies, ncRNAs are now presumed to be important regulators of gene expression. Based on their length, ncRNAs can be divided into short non-coding RNA (sncRNAs, <200 nucleotides) and long non-coding RNA (lncRNAs, >200 nucleotides). Because they are essential regulators of several genomic processes including gene expression, transcription, and post-transcription events, increasing evidence now suggests that lncRNAs are critical to cancer progression. Indeed, lncRNAs can have roles as signals, guides, scaffolds, and decoys [2].

Located on chromosome 4, lncRNA differentiation antagonizing non-protein-coding RNA (DANCR) is 855 base pairs in length and has a known function suppressing epidermal progenitor cell differentiation [3]. Importantly, new research now suggests that the oncogenic DANCR gene, which is overexpressed in various cancers, promotes malignant biological behaviors including cancer cell proliferation, invasion, metastasis, and chemo-resistance. Furthermore, DANCR is associated with poor patient prognosis and is emerging as a novel target for cancer treatment. This article reviews the regulatory roles of DANCR in tumor progression and the underlying mechanisms. The potential clinical value of DANCR targeting is also discussed, which may provide new insights into DANCR-based therapeutic approaches to treat cancer.

DANCR regulatory functions in tumor progression

New research has identified various regulatory roles for DANCR during tumor progression that are summarized in **Table 1**. Normally, DANCR acts as an oncogenic factor by promoting cancer cell proliferation, invasion, metastasis, chemo-resistance, epithelial-mesenchymal transition (EMT), cancer-stemness features, and angiogenesis.

Table 1. Function and mechanism of DANCR in human cancers

Cancer	DANCR expression	Regulated miRNAs	Regulated genes and proteins	Functional role
Osteosarcoma [13, 29, 31]	↑	miR-33a-5p	AXL	Proliferation↑Motility↑
	↑	miR-216a-5p	SOX5	Proliferation↑Motility↑Autophagy↑Apoptosis↓
	↑	miR-335-5p, miR-1972	ROCK1	Proliferation↑Motility↑
Nasopharyngeal carcinoma [8, 41]	↑	--	IL-6	Proliferation↑Motility↑
	↑	--	NF90/NF45, HIF-1α	Motility↑
Non-small cell lung cancer [32, 38, 54, 55]	↑	miR-138	SOX4	Growth↑Motility↑
	↑	miR-758-3p	--	Proliferation↑Motility↑
	↑	--	EZH2, p21	Proliferation↑Motility↑
	↑	miR-214-5p	CIZ1	Proliferation↑Apoptosis↓
Lung cancer [56]	↑	miR-216a	--	Proliferation↑Growth↑
Lung adenocarcinoma [9, 57]	↑	miR-496	mTOR	Proliferation↑Motility↑Apoptosis↓
	↑	--	HMGA2	Motility↑
Glioma [4, 5, 12, 18, 47, 58]	↑	miR-216a	LGR5	Proliferation↑Motility↑Angiogenesis↑Apoptosis↓
	↑	miR-33a-5p	--	Proliferation↑Motility↑EMT↑Apoptosis↓
	↑	--	Wnt/β-catenin	Proliferation↑Motility↑
	↑	miR-33a-5p, miR-33b-5p, miR-1-3p, miR-206 and miR-613	AXL	Chemo-resistance↑
	↑	miR-634	RAB1A	Proliferation↑
	↑	miR-135a-5p	BMI1	Proliferation↑Motility↑
Cervical cancer [19, 48, 59]	↑	miR-335-5p	ROCK1	Proliferation↑Motility↑
	↑	miR-665	TGFBR1	Proliferation↑Motility↑
	↑	--	FRAT1, FRAT2	Proliferation↑Growth↑
Ovarian cancer [25, 60, 61]	↑	miR-145	VEGF	Angiogenesis↑
	↑	--	IGF2	Proliferation↑Motility↑
	↑	--	UPF1	Proliferation↑Motility↑
Bladder cancer [20, 43]	↑	miR-149	MSI2	Proliferation↑Motility↑EMT↑
	↑	--	IL-11, LRPPRC, CCND1 and PLAU	Proliferation↑Motility↑
Prostate cancer [11, 62, 63]	↑	--	TIMP2/3	Motility↑
	↑	miR-135a	--	Chemo-resistance↑
	↑	miR-34a-5p	JAG1	Chemo-resistance↑
Breast cancer [15, 16, 45, 64]	↑	--	EZH2, SOCS3	Motility↑EMT↑Cancer stemness↑
	↑	miR-216a-5p	--	Proliferation↑Motility↑
	↑		RXRA, PIK3CA	Proliferation↑
	↑	--	EZH2, CD44 and ABCG2	Cancer stemness↑Proliferation↑Motility↑
Endometrial carcinoma [65]	↑	miR-214	--	Proliferation↑Apoptosis↓
Renal cell carcinoma [66]	↓	--	--	Proliferation↓Motility↓Apoptosis↑
Retinoblastoma [21]	↑	miR-34c, miR-613	MMP-9	Proliferation↑Motility↑EMT↑
Tongue squamous cell carcinoma [28]	↑	miR-135a-5p	KLF8, MMP-2/9	Proliferation↑Motility↑

Hepatocellular	↑	miR-27a-3p	ROCK1, LIMK1 and COFILIN1	Proliferation↑Motility↑Growth↑EMT↑
	↑	miR-216a-5p	KLF12	Proliferation↑Motility↑Apoptosis↑
Carcinoma [14, 23, 42, 67]	↑	miR-214, miR-320a and miR-199a	CTNNB1	Cancer stemness↑
	↑	--	PSMD10	Chemo-resistance↑
Colorectal cancer [6, 68]	↑	--	KAT6A	Proliferation↑
	↑	miR-577	HSP27	Motility↑Growth↑
Esophageal cancer [69]	↑	miR-33a-5p	ZEB1	Proliferation↑Motility↑
Gastric cancer [10, 37]	↑	--	lncRNA-LET, EZH2 and HDAC3	Motility↑
	↑	--	MDR1, MRP1	Chemo-resistance↑
Cholangiocarcinoma [70, 71]	↑	miR-345-5P	Twist	Proliferation↑Motility↑Angiogenesis↑EMT↑
	↑	--	EZH2, FBP1	Proliferation↑Motility↑
Pancreatic cancer [22, 72, 73]	↑	miR-135a	NLRP37	Proliferation↑Motility↑
	↑	miR-214-5p	E2F2	Proliferation↑Motility↑
	↑	miR-33b	MMP-16	Proliferation↑Motility↑EMT↑

Cell proliferation

DANCR affects cancel cell proliferation and apoptosis through cell cycle regulation. Specific DANCR-targeting small interference RNAs (siRNAs) that suppressed DANCR expression in glioma cells demonstrated that DANCR silencing increased G1 phase glioma cells and decreased the number of S phase cells to inhibit proliferation and increase apoptosis [4]. Another study with glioma cells reported that DANCR inhibition suppressed tumor proliferation and induced G0/G1 cell cycle arrest through altered miR-634 interactions that inhibited downstream expression of the protein, Ras-associated binding-GTPase 1a [5]. In the context of colorectal cancer (CRC), a study that used short hairpin RNA (shRNA) to knock down DANCR expression reported inhibited proliferation and cell cycle arrest due to decreased binding with lysine acetyltransferase 6A, which is a regulator of cell cycle-related proteins, including protein15 (p15) and p21. DANCR knockdown also altered chromatin by promoting the acetylation of histone H3 at lysine 23 [6].

Cell motility

Cell motility refers to the invasive and metastatic properties of cancer cells and is the major cause of cancer-caused deaths [7]. The role of DANCR in promoting cancer cell invasion and metastasis has been reported in several studies that investigated DANCR during tumorigenesis. For example, DANCR acted as a prognostic biomarker in nasopharyngeal carcinoma. DANCR also increased hypoxia inducible factor-1α mRNA stability through interactions with the nuclear factor (NF) 90/NF45 complex, which contributed to invasion and metastasis [8]. In addition, DANCR promoted lung adenocarcinoma cell invasion by positively regulating high-mobility group AT-hook 2, which is a mediator of cell motility [9].

Chemo-resistance

Although chemotherapy is a highly effective approach for cancer treatment, chemo-resistance ultimately leads to treatment failure in some advanced-stage patients. DANCR was shown to accelerate the development of multidrug resistance in gastric cancer cells [10]. Quantitative real-time polymerase chain reaction revealed that DANCR expression was significantly increased in cisplatin-resistant gastric cancer cell lines when compared to gastric cancer cell lines that were not cisplatin-resistant. Furthermore, after DANCR was knocked down using siRNA, the cisplatin-resistant gastric cancer cell lines exhibited decreased survival and increased apoptosis, which suggested that DANCR could be a therapeutic target to treat cancer. In prostate cancer, DANCR was strongly correlated with docetaxel resistance. DANCR promoted the downstream expression of the protein, Jagged 1, via sponging miR-34a-5p [11]. DANCR also reduced the sensitivity of glioma cells to cisplatin, which further reinforces that DANCR is a potential therapeutic target [12].

Cancer stemness

The cancer stem cell (CSC) hypothesis proposes that tumor-initiating cells are resistant to chemotherapy and drive tumor cell motility [13]. Notably, DANCR was shown to mediate cancer stemness by upregulating AXL receptor tyrosine kinase (AXL) through competitive binding to miR-33a-5p as part of the phosphatidylinositol 3-hydroxy kinase/protein kinase B (PI3K/AKT) signaling pathway. The upregulated signaling then promoted osteosarcoma progression [13]. In hepatocellular carcinoma (HCC), DANCR increased stemness features of HCC cells to promote tumorigenesis, which were attributed to an association with stemness-related mRNA for catenin beta 1 (also known as β-catenin) [14]. Moreover, a different study revealed that DANCR knockdown was associated with CSC marker gene repression due to increased binding of enhancer of zeste homolog 2 (EZH2) in the promoter region [15, 16]. DANCR was also upregulated in leukemia stem cells, and DANCR knockdown resulted in decreased stem cell renewal and quiescence [17]. Collectively, increasing evidence suggests that DANCR-based therapeutics may be a potential method to target CSCs.

Epithelial-mesenchymal transition (EMT)

EMT is directly related to the invasion and metastasis of malignant tumor cells. Numerous studies have shown that DANCR can mediate EMT [18-23]. For example, in cervical cancer, E-cadherin (epithelial) protein levels were significantly increased and vimentin (mesenchymal) levels were significantly decreased after

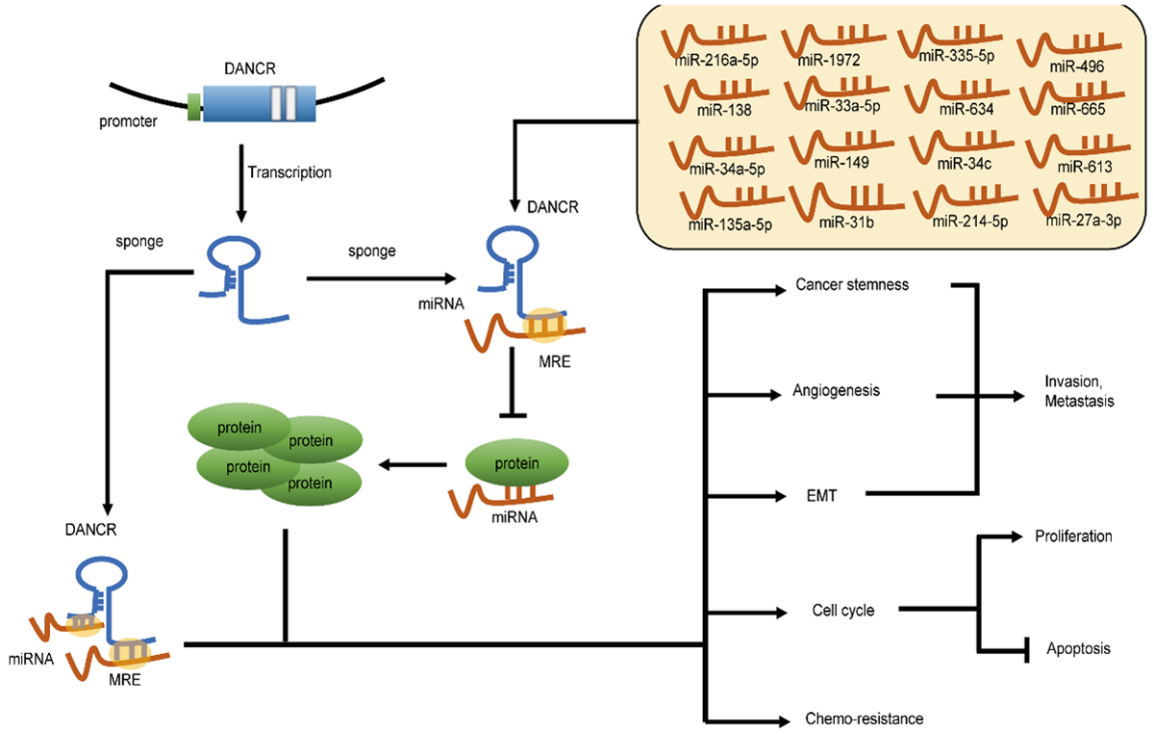

Figure 1. DANCR exerts oncogenic effects through sponging miRNAs and directly reversing their suppression of tumorigenesis. DANCR can also modulate tumor progression by promoting downstream protein expression after sponging the corresponding miRNAs.

DANCR was knocked down. The underlying mechanism was attributed to DANCR functioning as a competing endogenous RNA (CeRNA) that regulated Rho-associated coiled-coil forming protein kinase I (ROCK1) expression via sponging miR-335-5p [19].

Angiogenesis

In most malignant solid tumors, the formation of a large number of micro-vessels is the basis for tumor growth and metastasis and DANCR has been implicated in this process. Mechanistically, vascular endothelial growth factor (VEGF) is well-known to play a central role in promoting angiogenesis during the pathogenesis of diverse cancers [24]. For example, in ovarian cancer tissues, miR-145 downregulation inhibited VEGF suppression, which then promoted angiogenesis. Intriguingly, bioinformatics and a luciferase assay revealed that DANCR was an upstream regulator of miR-145 [25]. Tube formation assays in glioma cells also indicated that DANCR has a regulatory role in angiogenesis and that DANCR suppression can inhibit angiogenesis [4].

Underlying molecular mechanisms of DANCR regulation

The competitive endogenous RNA (CeRNA) hypothesis proposes that multiple RNAs including lncRNA, pseudogene transcripts, and circular RNAs have the same miRNA recognition elements (MREs); therefore, these RNAs could sponge the same miRNA to regulate the transcription and protein levels of target genes [26]. It was reported that DNACR acts in part through the CeRNA mechanism to regulate gene expression, which suggests that DANCR could relieve miRNA-related suppressive effects on target proteins by sponging corresponding miRNAs. Additionally, DANCR exerts oncogenic effects through sponging miRNAs and directly reversing their suppression on tumorigenesis (**Figure 1**).

Regulating miRNA and their targets through ceRNA effects

Matrix metalloproteinases (MMPs) are classical zinc-dependent endopeptidases that affect tumor cell proliferation, mortality, and angio-

genesis through extracellular matrix degradation [27]. A study that combined bioinformatics and a luciferase reporter assay revealed that miR-34c and miR-613 both targeted the 3'-UTR of DANCR and MMP-9. This correlation established the oncogenic role of the DANCR/miRNA/MMP-9 axes in retinoblastoma progression [21]. Similarly, noting that MMPs bind with Kruppel like factor 8 (KLF8), which is a downstream effector of DANCR/miR-135a-5p, researchers confirmed that MMP-9 and MMP-2 expression in tongue squamous cell carcinoma tissues was altered by the DANCR/miR-135a-5p/KLF8 axis [28]. MMP-16 is also targeted by the DANCR/miR-33b pathway in pancreatic cancer [22], which further illustrates the importance of MMPs in the DANCR related-molecular network.

ROCK1, which is a highly-expressed kinase in many tumors, is broadly reported to be involved in multiple important biological processes including cancer cell proliferation and apoptosis [29]. DANCR triggered ROCK1-mediated cell proliferation and lung metastasis in osteosarcoma by acting as a CeRNA of miR-335-5p and miR-1972 [29]. The importance of the DANCR/miR-335-5p/ROCK1 axis in tumorigenesis was also confirmed in cervical cancer [19]. In addition to its role in the DANCR/miR-335-5p axis, ROCK1 is also an upstream factor of LIM domain kinase 1 (LIMK1). LIMK1 is a serine/threonine kinase that regulates actin polymerization via phosphorylation and inactivation of the actin-binding factor cofilin 1 (CFL1); therefore, as a sponge for miR-27a-3p, DANCR could also exert oncogenic effects though the ROCK1/LIMK1/CFL1 pathway [23].

The sex determining region Y-related high-mobility group box (SOX) family of transcription factors are thought to regulate specific biological processes. Notably, the specific deregulation of gene expression programs correlates with cancer pathogenesis [30]. Indeed, recent studies demonstrated that overexpression of SOX family members, including SOX4 and SOX5, is linked to upregulated DANCR levels in cancer tissues [31, 32]. DANCR can promote SOX5-medicated progression and autophagy in osteosarcoma by sponging miR-216a-5p [31]. In non-small cell lung carcinoma, DANCR has been shown to compete with SOX4 mRNA to bind miR-138, which alters SOX4 expression to further enhance tumor growth and metastasis [32].

AXL is a member of the TAM receptor tyrosine kinase family and was originally identified as a transforming gene in leukemia cells. It is now considered to be important for tumor cell self-renewal, EMT, and chemo-resistance [33]. In glioma [12] and osteosarcoma [13], DANCR targeted AXL by binding to related miRNA to promote cancer stemness and chemo-resistance via the PI3K-AKT signaling pathway. Moreover, DANCR also promotes X-box binding protein I splicing (XBP1s) through miR-33a-5p via competitively combining with the 3'-UTR of XBP1 and regulates the expression of matrix metallopeptidase 13 (MMP13) by functioning as a sponge RNA for miR-1275 [34, 35].

Controlling gene transcription and signaling pathway by protein binding

DANCR exerts oncogenic effects through the regulation of numerous downstream genes and proteins (**Figure 2**). EZH2 is an oncogenic molecule that is closely related to various cancers. As a key element of polycomb repressive complex 2, EZH2 has an important role catalyzing the trimethylation of histone H3 lysine 27 and acetylation of histones H3 and H4 [36]. The upstream regulation of gene transcription by DANCR through EZH2 has been reported by several groups. For example, EZH2 can bind to histone deacetylase 3 (HDAC3) to form an epigenetic modifier that silences lncRNA-LET expression by binding to its promoter region and exerting histone modifications. RIP and RNA pull-down assays demonstrated that formation of the epigenetic modifier was mediated by DANCR overexpression in gastric cancer tissues and promoted cancer cell motility [37]. In non-small cell lung cancer (NSCLC), DANCR knockdown inhibited EZH2-mediated epigenetic silencing of the p21 promoter and increased p21 expression to inhibit cancer progression in a p21-dependent manner [38]. Except for EZH2, DANCR was also reported to activate the translation of FOXO3 mRNA by interacting with AU-binding factor 1 (AUF1) and promote EMT and fibrogenesis [39].

Interleukin/JAK/STAT signaling pathways

It is well established that the janus kinase-signal transducer and activator of transcription

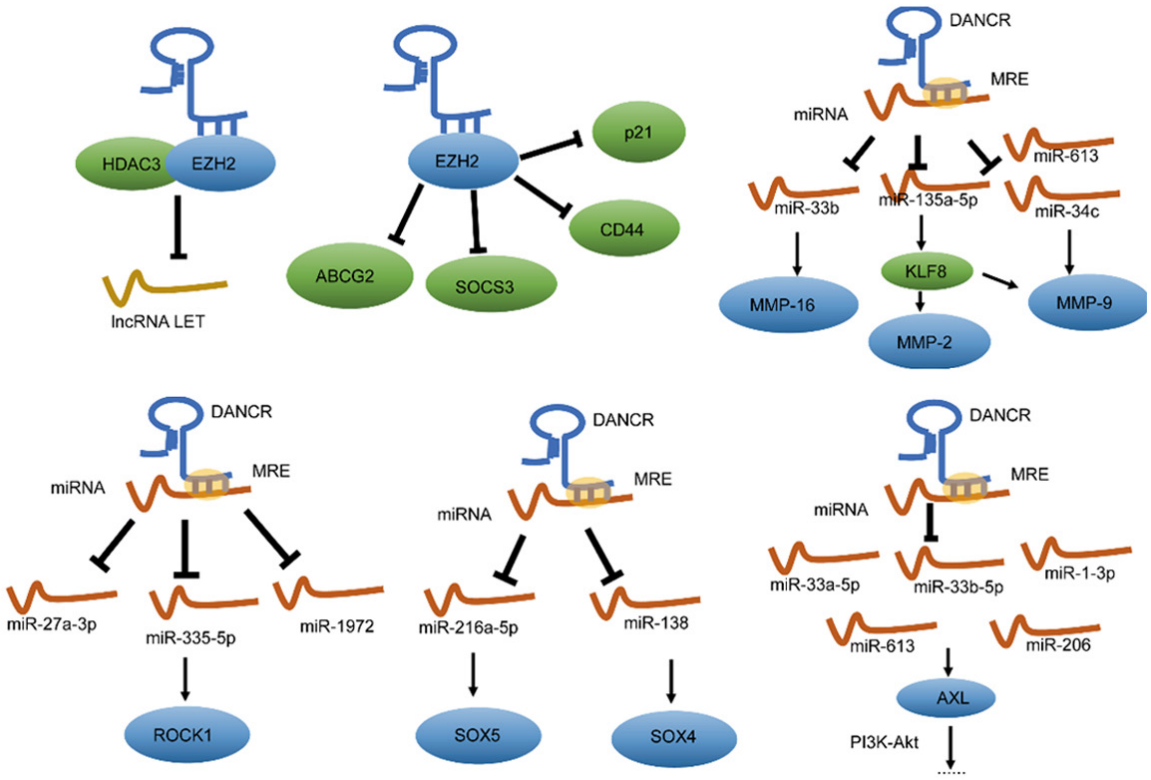

Figure 2. Genes and proteins regulated downstream of DANCR.

(JAK-STAT) signaling is involved in almost all immune regulatory processes, including cancer cell recognition and tumor-driven immune escape [40]. In nasopharyngeal carcinoma, DANCR promoted the proliferation and motility of cancer cells by stimulating the IL-6/JAK1/STAT3 signaling pathway. Mechanistically, DANCR bound to JAK1 and then mediated IL-6-induced JAK1/STAT3 stimulation, and the phosphorylation of STAT3 promoted the expression of oncogenic genes, including *c-myc*, survivin, *MMP-2*, and *IL-6* [41]. Additionally, the secretion of IL-6 in return created a positive feedback loop and further promoted the DANCR-mediated JAK1/STAT3 stimulation via increased STAT3 phosphorylation and DANCR transcription. Moreover, the function that DANCR exerted on chemo-resistance in HCC may also be explained by the activation of the IL-6/STAT3 signaling pathway, which was specifically motivated by the DANCR-induced stabilization of proteasome 26S subunit non-ATPase 10 (PSMD10) mRNA [42]. Also of note, in bladder cancer, DANCR interacted with leucine-rich PPR-motif-containing protein (LRPPRC) to stabilize IL-11 mRNA, and the resulting overexpression of IL-11 stimulated the phosphorylation of the JAK2/STAT3 signaling pathway, ultimately upregulating MMP-9 expression and promoting tumor progression (**Figure 3**) [43].

PI3K-AKT signaling pathway

The PI3K-AKT signaling pathway is a key target in oncology because it contributes to cancer cell proliferation, survival, and stemness [44]. Dysregulated PI3K-AKT signaling caused by oncogenic DANCR activity has been confirmed in diverse cancer types including osteosarcoma [13], glioma [4, 12], and triple negative breast cancer (TNBC) [45]. Decreased PI3K expression and AKT phosphorylation were observed after silencing DANCR.

Wnt/β-catenin signaling pathway

The Wnt/β-catenin signaling pathway is a well-characterized driver of cancer that promotes tumor progression by regulating the tumor immune cycle in various nodes, including immune and cancer cells [46]. After detecting decreased levels of proteins related to the Wnt/β-catenin signaling pathway (β-catenin,

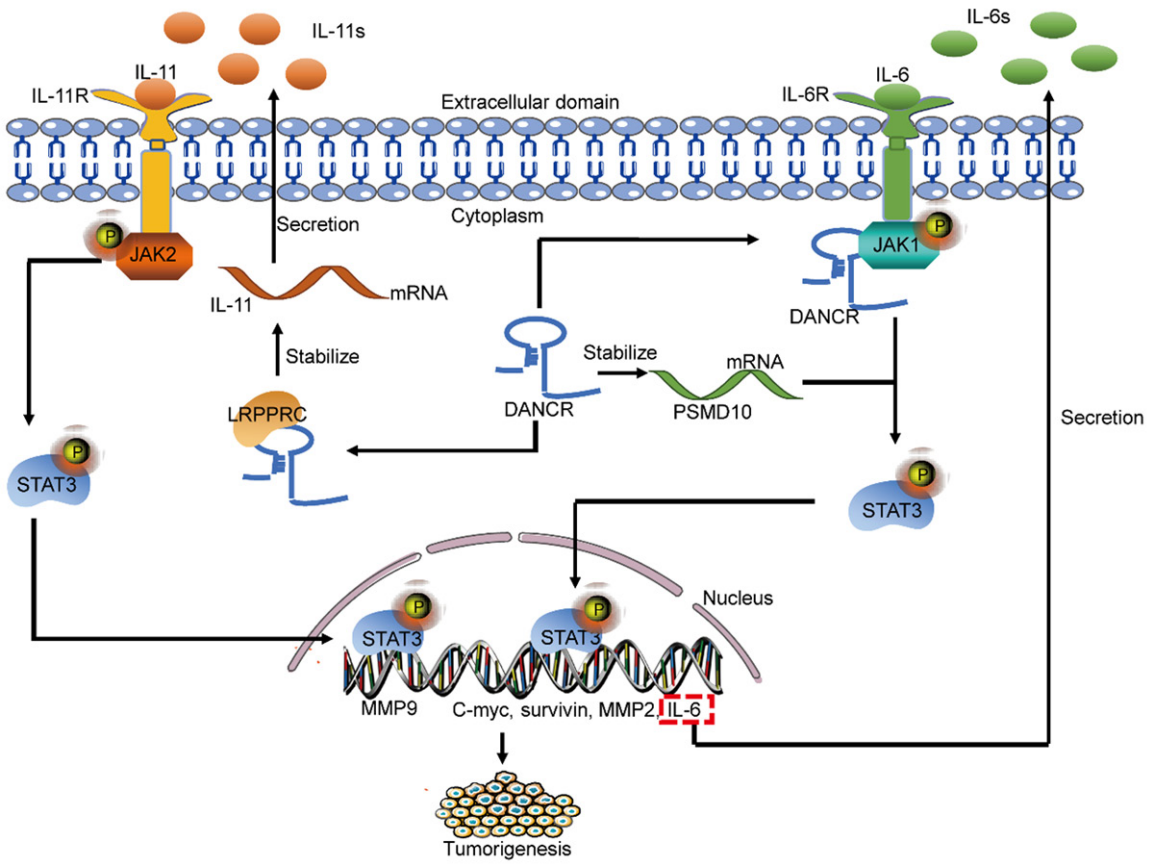

Figure 3. DANCR induces tumorigenesis and promote tumor progression through the activation of interleukins/JAK/STAT signaling pathways.

C-myc, and Cyclin D1), it was determined that DANCR promotes cancer cell proliferation and motility by activating Wnt/β-catenin signaling [47, 48].

DANCR-based therapeutic approaches in cancer treatment

As a prospective cancer treatment, lncRNAs are a promising option due to their collective therapeutic efficacy, high specificity, and minimal side effects. More specifically, because DANCR is an oncogenic factor that has a prominent role in various cancers, DANCR-based approaches to cancer treatment could be especially impactful and have already demonstrated preliminary efficacy. For example, DANCR siRNA was used to target CSCs for TNBC treatment [15]. The siRNAs induced DANCR silencing by complementing with the DANCR target, which led to target splicing and degradation. Widespread clinical use of this approach was impeded by low transfection efficiency and toxicity. To overcome these concerns, a systemic nanoparticle-mediated delivery system was developed in 2019. The nanoparticles are formed through self-assembly and include a multifunctional amino lipid, ECO, and DANCR siRNA. Additionally, polyethylene glycol within the nanoparticles improves biocompatibility and a cyclic RGD peptide facilitates tumor targeting for *in vivo* gene delivery [49]. The RGDPEG-ECO/siDANCR nanoparticles produced robust DANCR silencing in TNBC cells and significantly reduced proliferation, motility, survival, and tumor spheroid formation both *in vitro* and in nude mice bearing TNBC xenografts. Importantly, there were no overt toxic side effects with the nanoparticles, which suggests that it may be possible to develop a nanoparticle-mediated approach to modulate DANCR for cancer treatment.

DANCR can also be used as a biomarker cancer diagnoses and prognosis [50-52]. A recent study reported that the upregulation of DANCR was significantly correlated with poor prognosis

of patients with HCC [53]. Also, DANCR expression levels were significantly decreased in papillary thyroid cancer (PTC) tissues when compared to adjacent normal tissues. Further analysis indicated that DANCR expression was closely associated with PTC aggressive clinical features, including T grade (P<0.01) and TNM stage (P=0.017) [50]. A Kaplan-Meier analysis and a multivariate Cox model also showed that DANCR overexpression was an independent prognostic biomarker for CRC patients that was strongly associated with poor overall and disease-free survival [51]. Similar results were also reported for pancreatic ductal adenocarcinoma [52].

Despite its promise, DANCR targeting to treat cancer is still limited and requires further investigation.

Study limitations

A limited number of DANCR-associated studies prevented us from conducting a more comprehensive systematic review. Although DANCR is emerging as a promising therapeutic target for cancer, there are still many technical limitations that are associated with the newly discovered lncRNA. For example, its regulatory mechanisms remain unclear. Additional studies are needed to investigate the role of DANCR in cancer progression and to realize its full therapeutic potential.

Conclusion

In recent years, remarkable progress has been made in understanding the functions and detailed mechanisms of DANCR in tumor progression at the transcriptional and post-transcriptional levels. The mutual regulation between DANCR and its target genes, which is a new mechanism of regulating gene expression, has attached great importance to individual life processes. However, the interactions and complex regulatory mechanisms of the entire ncRNA network are still unclear, which indicates that further research is needed. Gradually elucidating the lncRNA-miRNA-mRNA regulatory network in cancer will help to make early, targeted clinical interventions. Furthermore, new knowledge about lncRNA regulation can help with early detection, diagnosis, and treatment, as well as accurate prognostic assessments. These new insights will also help to resolve chemo-resistance, radio-resistance, and other cancer-related treatment issues.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Yuting He, Department of Hepatobiliary and Pancreatic Surgery, The First Affiliated Hospital of Zhengzhou University, Zhengzhou 450052, Henan, P.R. China. Tel: +86-371-67967126; E-mail: fccheyt1@zzu.edu.cn; Drs. Shen Shen and Chen Xue, Department of Infectious Diseases, The First Affiliated Hospital of Zhengzhou University, Zhengzhou 450052, Henan, P.R. China. Tel: +86-371-67967126; E-mail: shenshenay@163.com (SS); zzuxuechen001@163.com (CX)

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