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Spotlight on the Expanding Role of DANCR in Tumorigenesis and Tumor Progression

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Abstract

Context: Long non-coding RNA (lncRNA) is a novel set of non-coding RNAs (ncRNA), over 200 nucleotides in length, accounting for the regulation of genes and chromosome structure. There are a few articles, mostly focusing on changes in the expression profile of DANCR. However, this review tried to collect documents to discuss the molecular mechanisms of this lncRNA in different cellular signaling pathways, considering microRNAs, to obtain a better understanding of its mode of action.

Evidence Acquisition: Differentiation antagonizing non-protein coding RNA (DANCR) is a cancer-associated lncRNA whose dysregulation, mostly upregulation, has been reported in almost all cancers, particularly in stages of invasion, migration, and progression. The regulatory mechanism of DANCR is mostly working as competitive endogenous RNAs (ceRNAs), leading to the hypothesis that lncRNA DANCR has oncogenic functions in malignancies. LncRNA DANCR harbors a number of MicroRNA Response Elements (MREs) for various microRNAs involved in different pathways, which are responsible for turning the situation toward supremacy for the dissemination of cancerous cells and ultimately metastasis, such as PI3K/Akt, TGF-β, Wnt, JAK-STAT, EMT, and DNA damages. In fact, lncRNA DANCR could potentially sequester microRNAs from their targeted mRNAs, which share the same MREs as DANCR.

Conclusion: This review article provides proper evidence, of why the aberrant expression of DANCR pathophysiologically turns the circumstances toward supremacy for the progression, migration, and invasion of cancerous cells, and proposes this lncRNA as a potent and extremely promising prognostic marker for the early detection of tumor progression and metastasis, as well as a therapeutic target for controlling the progression of several human malignancies.

Keywords: Biomarker, Cancer, DANCR, Long non-coding RNA, LncRNA

1. Context

The human genome reportedly includes about 20,000 genes encoding proteins, which account for <2% of the whole genome. In the genome of advanced eukaryotes, at least 70% of the sequences are transcribed into RNA. Most of these transcriptions are non-coding RNAs (ncRNAs) (1-5). Given the recent signs of progress in sequencing technology and the high-throughput sequencing of the genome on a larger scale, both short ncRNAs (containing less than 200 nucleotides) and long non-coding RNAs (lncRNAs, containing more than 200 nucleotides) are considered vital regulators in various human disorders (6-8). LncRNA is a category of ncRNAs, which is over 200 nucleotide sequences in length and does not have any information to code proteins. LncRNAs can control gene expression at the transcriptional, post-transcriptional, and epigenetic levels and are significant in several bioprocesses, including cell growth, differentiation, proliferation, survival, and migration. Many researchers have confirmed that abnormalities in the expression of lncRNAs can lead to various diseases in humans, especially cancer. Recently, studies have revealed that lncRNAs are of great importance in the onset and progression of conditions, and the number of lncRNAs present in the nucleus and cytoplasm is high (9-11). Among the critical advantages of lncRNAs that make them appropriate for cancer diagnostic and prognostic biomarkers, their high stability in body fluid circulation, especially when exposed to apoptosis or exomes, is a significant feature. Some findings indicated that despite the high presence of ribonucleases in various body fluids, lncRNAs could be found in these specimens. They can resist the destructive activity of ribonucleases (12). In addition to the primary tissues of the tumor, impaired regulation of lncRNAs is observed in body fluids such as plasma, whole blood, serum, urine, and saliva (13). The development of non-invasive methods is essential for identifying biomarkers that provide patients with better tolerance to conventional tissue biopsy. Non-invasive methods to detect cancer-related lncRNAs in body fluids can be used to evaluate tumor grades in patients with high sensitivity and specificity (14). LncRNAs are reportedly crucial molecules in the development of numerous tumors in humans (15).

Differentiation antagonizing non-protein coding RNA (DANCR), also known as anti-differentiation non-coding RNA (ANCR), is a human lncRNA positioned on chromosome 4; the closest adjacent annotated genes to this region are USP46 and

ERVMER34-1 (16). The prediction of the best secondary structure of the lncRNA DANCR with a minimum free energy (MFE) of −414 kcal/mol and a dot-bracket notation was designed using an R-fold webserver (Vienna package, http://rna.tbi.univie.ac.at/cgi-bin/RNAWebSuite/RNAfold.cgi) (Figure 1). According to recent studies, lncRNA DANCR has increased in various cancers, highlighting its potent diagnostic power for cancer therapy (Figure 2). The expression and critical roles of DANCR in the polycystic kidney are still unknown (17). MicroRNAs, as the smallest ncRNA molecules (comprising about 22 nucleotides), play a role in silencing RNA and regulating gene expression post-transcriptionally in animals, plants, and some viruses. LncRNAs can sponge microRNAs and suppress their effects (18).

The biological functions of DANCR in various cancers are summarized in (Table 1) A schematic representation of the regulatory mechanisms of upstream and downstream DANCR in cancer and the relation between DANCR and miRNAs and their target genes in cancer are shown in (Figure 3).

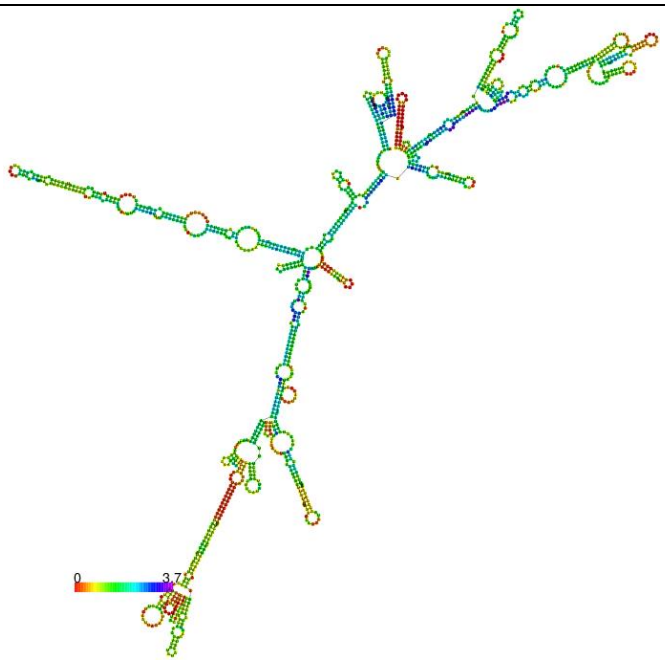

Figure 1. Prediction of the optimal secondary structure of the lncRNA DANCR (EPS format) with −414.90 kcal/mol with its dot-bracket notation using the R-fold web server

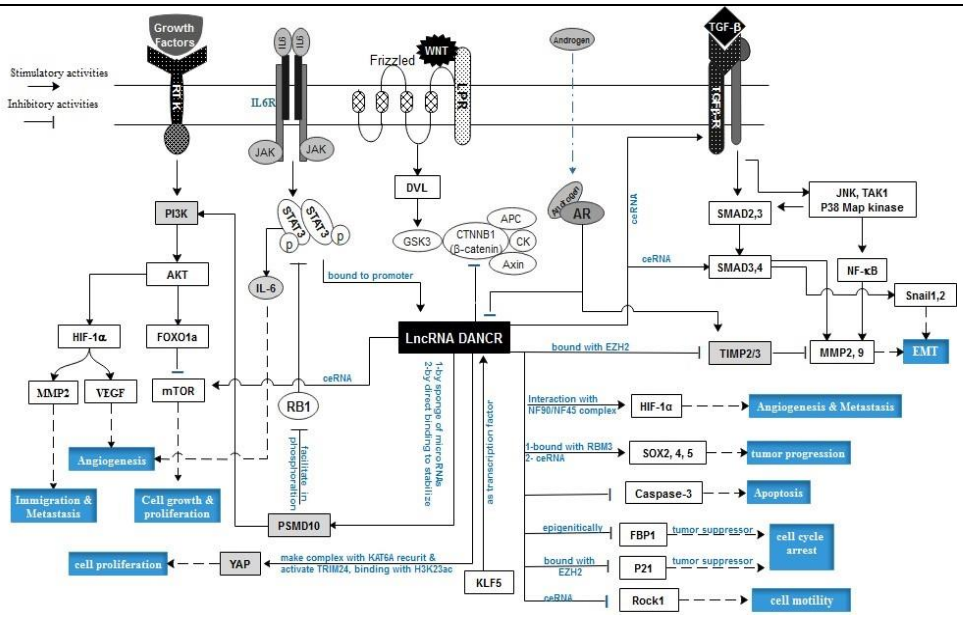

Figure 2. Schematic representation of the regulatory mechanisms of upstream and downstream DANCR in cancer

Table 1. Dysregulations of DANCR and its target gene in various cancers

Cancer type	Expression	Targeted microRNAs	Effected genes	Ref.
Hepatocellular Carcinoma	Upregulation	miR-214, miR-199a, miR-320a, miR-216a-5p, miR-605, miR-1254	CTNNB1	(16-25)
Prostate cancer	Upregulation	miR-135a, miR-214-5p, miR-34a-5p, miR-185-5p	TIMP2/3	(31-36)
Breast cancer	Upregulation	miR-216a-5p, miR-4319, miR-758-3p, miR-874-3p	CD44, ABCG2	(41-47)
Gastric cancer	Upregulation	lncRNA-LET, miR-194	-	(42, 51)
Colorectal cancer	Upregulation	miR-577, miR-145-5p, miR-518a-3p	TRIM24, Caspase 3	(56, 60)
Lung cancer	Upregulation	miR-496, miR-216a, miR-214-5p, miR-138, miR-1225-3p	P21, mTOR	(68-72)
Osteosarcoma	Upregulation	miR-33a-5p, miR-335-5p, miR-1972, miR-149	ROCK1, AXL,	(80-84)
Pancreatic cancer	Upregulation	miR-33b, miR-214-5p	MLL3	(88-90)
Retinoblastoma	Upregulation	miR-34c, miR-613	MMP-9	(92)
Glioma	Upregulation	miR-634, miR-135a-5p, miR-33a-5p	RAB1A	(94-96)
Renal cell cancer	Downregulation	miR-3646, miR-634	-	(101)
Lymphoma	Upregulation	-	p21 (CDKN1A)	(106)
Bladder cancer	Upregulation	miR-149, miR-335	MSI2, CCND1, IL-11, PLAU	(110-112)
Cervical cancer	Upregulation	miR-665, miR-335-5p, miR-145-3p		(132-134)
Nasopharyngeal carcinoma	Upregulation	-	RBM3, NF90/NF45	(140, 141)
Cholangiocarcinoma	Upregulation	-	FBP1	(145)
Esophageal squamous cell carcinoma	Upregulation	miR-4707-3p	-	(148)
Acute myeloid leukemia	Upregulation	miR-874-3P	-	(152)

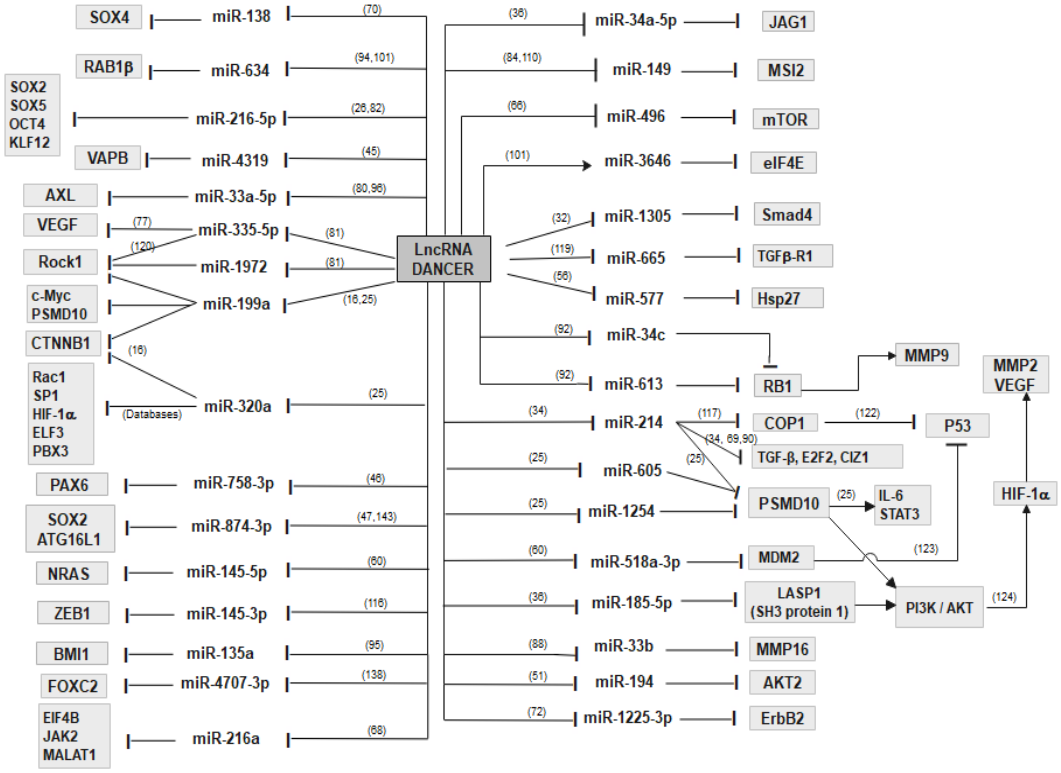

Figure 3. LncRNA DANCR functions as a ceRNA to sponge many microRNAs involved in different pathways and consequently causes dysregulation in genes such as the TGF-β receptor pathway, the PI3K-Akt pathway, the apoptosis signaling pathway, the JAK-STAT signaling pathway, the developmental pathway, the mTOR signaling pathway, the MAPK signaling pathway, the VEGF signaling pathway, the Wnt signaling pathway, and Smad signaling, which are targeted by these microRNAs. The targeted genes are shown in gray rectangles

2. Hepatocellular Carcinoma

Hepatocellular carcinoma (HCC), the reason for the annual death of 600,000 people, is the third global cause of death from cancer. Infection with hepatitis B (HBV) and C (HCV) viruses is a leading

contributor to HCC development. The poor prognosis and high recurrence rate of this type of cancer are mainly related to intra-cerebral and bone metastases at the beginning of HCC (19). HCC is common in Africa and East and Southeast Asia. Surgery and liver transplantation are the best strategies for treatment. Due to liver weaknesses caused by hepatic dysfunction and cirrhosis, only 1% of patients with HCC are eligible for surgical measures, and transplantation is restricted due to donor deficiency (20, 21). Since the diagnosis of most patients with HCC occurs during the late stage of the disease, this is the best time for surgical removal. Metastasis and recurrence are often diagnosed in subjects undergoing surgical procedures, and the five-year survival rate after surgery is estimated to be 30-40% (22). The high recurrence rate and weak prognosis are mainly related to intra-cerebroventricular and extra-liver metastases in early-stage HCC. Therefore, it is essential to investigate the main molecular mechanisms responsible for the beginning and progression of HCC and select novel biomarkers for therapeutic purposes. One of these biomarkers is the lncRNA DANCR. The increase in DANCR expression could be associated with tumorigenesis and the colonization of intra- and extra-hepatocyte tumors in HCC. In addition, DANCR is involved in maintaining and regulating the characteristics of liver cancer stem cells. Accordingly, DANCR can act as a unique target to determine the biology and healing of HCC. Plasma levels of DANCR are far greater in chronic HCV+ patients and even more increased in HCV patients than in subjects suffering from cirrhosis or chronic HBV+. Additionally, the diagnostic power of DANCR in plasma can be a better diagnostic index than the diagnostic amount of alpha protein to distinguish patients with HCC (23). Wnt signaling pathways are a collection of signal transduction cascades involving highly conserved protein kinases that transmit cellular signals to the cell through cell surface receptors. For the first time, the function of carcinogenesis was reported for this signaling pathway, followed by identifying a role in embryonic development (24). The DANCR expression level in biological samples, such as serum, has been verified. Targeted molecular therapy has specific benefits for tumors, and its systemic toxicity is low. Further studies showed that DANCR acts as a competitive endogenous RNA (ceRNA) in enhancing liver cancer stem cells through the expression of CTNNB1 (coding a protein named β-Catenin involved in cell-cell adhesion and transcription) and inducing the Wnt pathway through competition between CTNNB1 and microRNAs of miR-199a, miR-320a, and miR-214 (16). LncRNA DANCR enhances sorafenib resistance through the activation of IL-6/STAT3 signaling in HCC cells via PSMD10. PSMD10 could induce angiogenesis via the upregulation of VEGF and MMP2 through the PI3K-AKT-HIF1α pathway. Liu *et al.* (2021) also showed that not only does lncRNA DANCR contain MicroRNA Response Elements (MREs) that can sponge miR-214, miR-1254, miR-199a, miR-605, and the targeted 3'-UTR of PSMD10 mRNA, but it can also directly interact with the mRNA of PSMD10, which ultimately increases the mRNA stability of PSMD10. They also found positive feedback between IL-6/STAT3 and DANCR expression. PSMD10 can induce the IL-6/STAT3 signaling pathway by assisting in the phosphorylation of RB1 and consequently the upregulation of IL-6. On the other hand, it was found that the promoter of DANCR contains a STAT3-binding site, and thus phosphorylated STAT3 can induce the transcription of DANCR (25).

On the other hand, in another experiment, conflicting results were obtained in HCC using a dual-luciferase reporter and radio-immunoprecipitation assay. The *in vivo* experiment has confirmed that the Kruple-like factor 12 (KLF12)/miR-216a-5p interaction plays a vital role in different types of tumors. The results revealed that DANCR could significantly suppress cell proliferation and tumor growth *in vivo* by decoying the miR-216a-5p (26).

2.1. Prostate Cancer

Prostatic cancer (PC) affects one in every nine men over the age of 65, with the highest prevalence among American males (27). Although radiotherapy and surgery are generally useful for most men, the prognosis for patients with this progressive disease is disappointing (28). PC cells are highly susceptible to metabolic changes and cancerous genes that alter metabolic hemostasis (29, 30). The Tissue Inhibitor of Metalloproteinase 2/3 (TIMP2/3) gene, a member of the TIMP gene family, encodes a protein that acts as a metastatic suppressor (31). According to the literature, DANCR expression levels are higher in cancer and prostate tissues than in healthy prostate tissues and cells. TIMP2/3, which inhibits prostate metastasis, is reduced by DANCR in synergy with the histone methyltransferase Enhancer of Zeste homolog 2 (EZH2) through epigenetic silencing of the promotor. The expression of DANCR has been suppressed by the signaling pathway of the androgen receptor (AR) and the TIMP2/3 elevations. Moreover, increasing the lncRNA DANCR inhibits TIMP2/3 upregulation. On the other hand, it was found that the expression of the lncRNA DANCR is influenced by the androgen-AR signaling pathway. Treating the prostate cancerous cell with dihydrotestosterone decreases the lncRNA DANCR level (31).

Zhang *et al.* (2017) revealed that miR-1305 antagonizes the function of DANCR. The overexpression of miR-1305 resulted in the downregulation of the transforming growth factor-beta (TGF-β) pathway member Smad4 (32). Zhao *et al.* (2019) reported that the downregulation of

DANCR converges with increasing paclitaxel sensitivity in PC cells by the negative regulation of miR-135a (33). It was indicated that the DANCR/miR-214-5p/TGF-β axis regulatory network plays a key regulatory role in PC progression, and they suggested the ability of this axis as a maker in the screening and treatment of patients (34). It was also found that DANCR causes the upregulation of JAG1 by sponging miR-34a to induce docetaxel resistance in PC (35). Sun *et al.* (2021) showed that DANCR exerts oncogenic roles in PC via the miR-185-5p/LASP1 axis, activating the FAK/PI3K/AKT/GSK3β/Snail pathway. Therefore, it can be a potential biomarker in the diagnosis and monitoring of PC (36).

2.2. Breast Cancer

Breast cancer is one of the leading malignancies among females worldwide, causing 23% of all new cases of cancer and 14% of all deaths in 2008 (37, 38). Although significant improvements have been made in early detection and targeted therapies in recent years, the specific cause of breast cancer is still unclear (39). Therefore, studies to determine the molecular mechanisms of genetic tumors and the progression of breast cancer are essential for diagnosis, prognosis, and treatment in the future. Breast cancer is one of the most dangerous human hormonal cancers, and disruptions in estrogen receptor (ER) regulation are involved in approximately 75% of total breast cancer (40). A study found an increase in DANCR expression in neoplastic triple-negative breast cancers (TNBCs) and reported a correlation between its high expression with TNM (Tumor, Node, and Metastasis) stages and overall survival. Studies on molecular mechanisms have revealed that DANCR destruction is accompanied by an increase in EZH2 (the catalytic subunit of the Polycomb Repressive Complex 2) binding to CD44 and ABCG2 proteins, and the simultaneous reduction of these gene expressions suggests that targeting the expression of DANCR may be an appropriate therapeutic approach for treating TNBC (41). DANCR is used with EZH2 and histone deacetylase 3 for regulating the migration and invasion of GC through the lncRNA-LET epigenetic silencing (42). A study aimed to investigate the crosstalk between DANCR and cytokine signaling inhibitor 3 (SOCS3) in breast cancer and showed that DANCR regulates the inflammatory breast cancer cells and contributes to the progression of breast cancer by suppressing SOCS3 transcription due to EZH2 (43). In another study, miRNA-216a-5p was predicted as a DANCR target by bioinformatics analysis. For an in-depth understanding of this molecular mechanism, practical experiments were performed *in vivo* in two breast cancer cell lines (MCF-7 and MDA-MB-231). The results showed that DANCR, by targeting miRNA-216a-5p, reduces the inhibitory effect of miRNA-216a-5p on the expression of Nanog, SOX2, and OCT4 genes, acting as a tumor promoter and causing tumorigenesis and invasion in breast cancer (44). Jia *et al.* (2020) also reported the role of the lncRNA DANCR in increasing the proliferation and metastasis of breast cancer cells through sponging miR-4319 and upregulating VAPB (45). Zhang *et al.* (2020) stated that the molecular network of lncRNA DANCR/miR-758-3p/PAX6 has a role in the regulation of apoptosis in breast cancer cells (46). It was observed that the upregulation of DANCR by TUFT1 led to the promotion of breast cancer progression through the miR-874-3p-SOX2 axis (47).

2.3. Gastric Cancer

Gastric cancer (GC), which has a mortality rate of 75%, has been reported as the third reason for cancer deaths. Although the initial treatment of GC has been successful, because of the absence of proper biomarkers for early diagnosis, the survival rate is still low. Both carcinoembryonic antigens and CA125 are clinically potent markers but have dissatisfaction with specificity and sensitivity, even in their combined form. Therefore, a new molecular diagnosis is necessary for the early detection of such a risky condition (48). A study confirmed that high DANCR expression and low lncRNA-LET levels in tissue samples extracted from GC patients, compared to healthy controls, are significantly associated with metastatic lymph node disease and end-stage illness. It was also shown that DANCR is involved in the progression of the migration and invasion of GC via suppressing the lncRNA-LET (42). Hao *et al.* (2017) employed the qRT-PCR technique and reported an increase in the lncRNA DANCR at the transcriptional level in GC tissue samples compared to non-cancerous tissues and an increase in GC. Therefore, DANCR can represent a potential biomarker of poor prognosis and a strong therapeutic target in the treatment of GC (49). Pan *et al.* (2018) reported that DANCR is activated by SALL4 in GC cells and exerts its oncogenic activities through the activation of the β-catenin pathway. Taken together, our findings suggest that DANCR promotes the progression of GC and has the potential to serve as a novel diagnostic biomarker. They considered an oncogenic role via the activation of the β-catenin pathway (50). Cheng *et al.* (2021) revealed the activation of lncRNA DANCR disturbed in KLF5 knockdown GC cells, which led to the upregulation of miR-194 (51).

2.4. Colorectal Cancer

Colorectal cancer (CRC), with a prevalence of over 1.2 million new cases annually, is one of the most prevalent cancers among humans. Although there are valuable documents on the molecular mechanisms and progression of CRC in chemotherapy, radiotherapy, and surgical procedures, the overall survival rate and prognosis of CRC are still poor. Only

a limited number of potent genes have been introduced as biomarkers or factors for clinical diagnosis. However, there is a need for future research regarding the identification of new biological factors with this capability to be used as reliable prognostic markers with enough sensitivity and specificity to detect the progression of CRC and even be considered new therapeutic targets (52-54). The high DANCR expression level was associated with histologic degree, lymph node metastasis, and TNM stage. The results indicated that the research units with high DANCR expression levels have shorter OS and disease-free survival, compared to groups with low DANCR expression levels. Accordingly, Liu *et al.* (2015) suggested that the level of DANCR may be considered a strong biomarker for the prognosis of CRC (55). Wang *et al.* (2018) reported the overexpression of the lncRNA DANCR in CRC. They revealed that DANCR functions as a ceRNA to sponge miR-577. They also reported that the knockdown of the lncRNA DANCR converges with the depression of Hsp27. Hsp27 is involved in cell proliferation and metastasis through the activation of AP1 and influencing epithelial-mesenchymal transmission (EMT), respectively. They justified this phenomenon using bioinformatics tools to detect the common MRE for miR-577 on lncRNAs DANCR and Hsp27. The overexpression of Hsp27 in favor of CRC progression was argued via sponging miR-577 by up-regulated DANCR (56). It was also reported by Yang *et al.* (2018) that apoptosis, by promoting caspase-3, increases in DANCR-knockdown colon cancer cells and significantly impairs cell proliferation as well as tumor growth (57). TRIM24 is significantly overexpressed in CRC due to its amplification. Increasing the level of TRIM24 was negatively correlated with decreasing the survival rate of patients (58). Xie *et al.* (2020) revealed that the complex of DANCR/KAT6A can recruit and activate TRIM24, which is bound to H3K23ac in the promotor of YAP, resulting in the promotion of YAP and signaling to increase cell proliferation (58). Sun *et al.* (2020) provided evidence for the attenuation of growth and metastasis by the knockdown of the lncRNA DANCR in colon cancer cells. They described that DANCR acts as a ceRNA to sponge miR-518a-3p. This microRNA targets MDM2 mRNA in the cytoplasm, where the level of MDM2 (and its human homolog HDM2) increases. MDM2 (or HDM2) are mediators that negatively regulate p53 (59). Bahreini *et al.* (2021) measured the sensitivity and specificity of DANCR, miR-145-5p, and NRAS by ROC curve analysis and stated that these factors could be considered useful biomarkers for screening colorectal neoplasms (60).

2.5. Lung Cancer

Lung cancer has also been known as the main reason for global mortality, and in 2012 alone, there were about 1.5 million deaths caused by it. In Europe, lung cancer causes 353,000 deaths annually, accounting for approximately 20% of total cancer deaths. Non-small-cell lung carcinoma (NSCLC) is responsible for approximately 80% of new lung cancer cases and is the main type of cancer with a poor prognosis in chemotherapy. Therefore, there is a need for molecular targets and prognostic biomarkers for lung cancer (61-64). Lung cancer screening via low-dose CT in high-risk individuals, compared to those in the chest radiograph, can reduce the mortality of lung cancer by more than 20%. However, early diagnosis of cancer does not reduce mortality, which means that screening is not beneficial in these ways (65). Recently, it has been shown that DANCR, as an oncogenic lncRNA and endogenous RNA (ceRNA), plays an essential role in regulating mTOR expression levels by directly binding to miR-496 (66). Furthermore, an *in vivo* experimental study using an NPs-based siRNA delivery technique to target the lncRNA DANCR, confirmed that the DANCR expression level is significantly correlated with tumor size and suggested that DANCR could be considered a potential therapeutic target and biomarker to deal with antibody-drug conjugates (67). DANCR dysregulation has been observed in lung cancer, especially in aggressive cancer cells and high-grade lung cancer tissues. The extracorporeal expression of DANCR induces the proliferation of lung cancer cells and the formation of colonies, whereas knocked-down DANCR induces the opposite impacts. The miR-216a level in cancer cells is negatively linked to DANCR expression. The targets of miR-216a, such as EIF4B, JAK2, and MALAT1, could therefore be upregulated by increasing the level of the lncRNA DANCR. The *in vivo* examination of xenografts also showed that silencing the DANCR promotes tumor growth. Zhen *et al.* (2018) also proposed that the overexpression of DANCR may be a potent index of invasive lung cancer. Therefore, the knockdown of DANCR may serve as an essential target for the management of lung cancer (68).

Chen *et al.* (2020) induced apoptosis in NSCLC cells by silencing the lncRNA DANCR. They found that DANCR can act as ceRNA to sponge miR-214-5p. On the other hand, the CIZ1 targeted by miR-214-5 is known as the driver of tumor growth. They perceived that lncRNA DANCR could function as an oncogene through the regulation of miR-214-5p, which leads to the upregulation of CIZ1 as an oncogene working in cell proliferation and cell cycle progression (69). Bai *et al.* (2019) found that SOX4 is bound to the promoter regions of the DANCR gene to increase DANCR expression and is targeted by miR-138. On the other hand, they stated that miR-138 could be sponged by DANCR. Therefore, they suggested this positive feedback loop of DANCR/miR-138/SOX4 for the progression of NSCLC (70). Guo *et al.* (2019)

showed that EZH-2-mediated epigenetic silencing of the p21 promoter is impacted when the lncRNA DANCR is knocked down by siRNA. This increases the level of p21 and controls NSCLC cell proliferation, migration, and invasion (71). Huang *et al.* (2021) revealed that DANCR promotes ErbB2-mediated migration and invasion via working as a ceRNA of miR-1225-3p in NSCLC cells (72).

2.6. Osteosarcoma

Osteosarcoma (OS) is one of the most prevalent malignant tumors of the bone among young adults, adolescents, and children (73), developing predominantly adjacent to bone growth and reconstruction areas. Recent findings suggest OS development by epigenetic and genetic modifications dissolves mesenchymal stem cells to be distinguished from osteoblasts (74). In the last decades, the results of patients showing improvements in the treatment of the OS have improved (75), leading to a remarkable increase of 60-70% of OS patients with an overall rate of five-year survival. However, the results are still incomplete, and a majority of patients die because of pulmonary metastasis or recurrence after chemotherapy and surgery (76, 77). Numerous recent clinical parameters, such as response to chemotherapy, surgical margin, and tumor size, have been considered prognostic markers for OS patients. The lack of sensitivity and specificity of these tests suggests that various genetic mechanisms may be used to alter the reaction to chemotherapy and metastatic capacity in several tumors at the same clinical stage (78). Therefore, accurate screening is needed for patients with osteosarcoma with a poor prognosis, including precise molecular markers for prognosis and early treatment. The OS is a primary bone malignancy, mainly in long bones and occasionally in soft tissues. This two-way distribution with peaks is mainly obtained in life's second decade, at the end of adulthood (79). There is a significant upregulation in the DANCR in OS tissues, which has a direct correlation with metastasis and tumor as an individual factor for prognosis. DANCR mediates the overexpression of the receptor tyrosine kinase AXL by binding competitively to miR-33a-5p, which strongly indicates a surveillance network in the OS (80). An animal model that studies the role of DANCR in the OS cancer metastasis revealed that DANCR and ROCK1 have been significantly upregulated. Afterward, using a luciferase reporter, it was shown that DANCR induces tumor growth and lung metastasis by regulating ROCK1 through miR-335-5p and miR-1972 sponges (81). Silencing the DANCR indicated that this lncRNA could prevent SOX5-medicated development and autophagy in OS by sponging miR-216a-5p (82). It was also found that Wnt/CTNNB1 is one of the signaling pathways activated by the lncRNA DANCR for osteoblast differentiation. Therefore, Jiang *et al.* (2019) suggested that DANCR may be a potential predictor and biomarker for future prognosis and the new objective of treatment for OS (83). Zhang *et al.* (2020) showed that the lncRNA DANCR plays the role of a ceRNA for miR-149. Musashi RNA-binding protein 2 (MSI2) mRNA is targeted by miR-149. The MSI2 gene encodes a translational regulator that targets the cell cycle regulator genes. Even they suggested DANCR as a potential target to control OS (84).

2.7. Pancreatic Cancer

Pancreatic adenocarcinoma cancer (PDAC) is a lethal diagnosis for most patients. This type of cancer alone accounted for 43,140 new cases and the deaths of 36,800 people in the United States in 2010 (85). Despite numerous studies on this disease in the past few decades, therapeutic regimens, chemotherapy, and radiation therapy have been mostly ineffective (86). Although surgery is the only way to treat it, only 15-20% of patients with pancreatic cancer at the time of delivery are eligible for successful surgeries. The survival expectancy is five years, and the survival rate is 23-21% (87). Studies have shown that the overexpression of the lncRNA DANCR in PDAC is associated with the progression of cancer and the prognosis of overall and progression-free survival rates. DANCR can increase the proliferation and metastasis of PDAC cells and be used as a prognostic marker and treatment target in PDAC (88). Luo *et al.* (2020) stated that DANCR exerts its function by sponging miR-33b, which could target MMP16. In fact, the upregulation of the lncRNA DANCR converges with MMP16, which is involved in the dissemination and invasion of cancerous cells (88). Liu *et al.* (2020) showed that MLL3 is overexpressed in the initial pancreatic cancer to restrict cancer progression, in which DANCR has no role in regulating MLL3, but in advanced stages, it downregulates MLL3 (89). Yao *et al.* (2019) obtained data to show that lncRNA works as an oncogene. They found that DANCR exerts its effect through the axis of lncRNA DANCR/miR-214-5p/E2F2 involved in development. They suggested that this axis might provide a potential target for pancreatic cancer therapy (90).

2.8. Retinoblastoma

Retinoblastoma (RB) is one of the pediatric eye cancers, with a mortality rate of about 50-70%. It is hard to timely detect and manage this cancer because of unknown pathological changes in parents and their children (91). The DANCR functions as a ceRNA for miR-613 and miR-34c, which have a role in the control of metastasis and progression of RB by targeting MMP-9. The DANCR is reportedly dysregulated in RB cells and tissues and is involved in the biology of RB tumor progression. The findings on the role of DANCR in RB carcinogenesis suggest a therapeutic viewpoint of the miR-34c/miR-

613/MMP-9 axis for this cancer (92).

2.9. Glioma

Glioma is a type of deadly tumor that starts in the central nervous system of adults, with a prevalence of 5 cases per 100,000 people per year. Although progress has been made in various therapies, including chemotherapy, radiotherapy, and surgery, the overall survival rate of most patients with gliomas, in particular glioblastomas, is obscure. Most recent investigations have demonstrated that lncRNAs have an essential function in the development of gliomas (93). DANCR overexpression is significant in glioma cell lines and tissues (U87MG, LN229, U118, and U251). The higher expression level of DANCR has a correlation with advanced-grade tumors, tumor growth, and the progression of the cell cycle from G0/G1 to the S phase. RAB1A is a target gene of miR-634 and has a key role in tumor progression. The results showed that DANCR increases the expression level of RAB1A by trapping miR-634 in the glioma cells. DANCR, through this mechanism, acts as an oncogene in the progression of glioma and could be considered a potential therapeutic target to treat patients with glioma (94). The inhibition of glioma cell proliferation, migration, and invasion were achieved by knocking down lncRNA DANCR. Feng *et al.* (2020) justified their obtained data due to sponging the miR-135a-5p, which by itself can target the mRNA of BMI1, a polycomb ring finger oncogene able to suppress p53 and be rapidly recruited in the sites of DNA damage (95). Yang *et al.* (2018) reported that silencing DANCR increases the level of miR-33a-5p and consequently reduces EMT and induces apoptosis (96).

2.11. Renal Cell Carcinoma

Renal cell carcinoma (RCC) is a common form of kidney cancer that occurs predominantly in adults, accounting for 3% of all malignant tumors and 85% of renal tumors (97, 98). RCC is the third cause of urinary tract cancers with the highest mortality rate after prostate and bladder cancers (99, 100).

Downregulation of the lncRNA DANCR in RCC tissues was reported by Jin *et al.* (2017). By transfection of a vector expressing the lncRNA DANCR, it was confirmed that DANCR impedes cell invasion, proliferation, and migration and induces apoptosis in transfected cells. By using bioinformatics and prediction tools, they computationally justified their findings, revealing that lncRNA DANCR could be regulated mostly by miR-3646 and miR-634. It is clear that further studies are required to work on the association of the lncRNA DANCR with miR-3646 and miR-634 (101).

2.12. Lymphoma

Lymphoma is a lymphatic system cancer that affects the lymphocytes in the immune system. This type of cancer is often curable and can be seen at any age, but predominantly in children and adolescents. Lymphocytes are placed in the bone marrow, thymus, spleen, and lymph nodes. In lymphoma conditions, lymphocytes change and get out of control (102). Lymphoma is a general term that includes a large group of cancers that often originate from lymph nodes. Due to changes or mutations in the lymphocyte, a proliferation of uncontrollable cells results in tumor necrosis in lymph nodes (103). Cell cycle progress is a series of events governed by highly conserved cyclin-dependent kinases (CDKs) that are regulated by CDK inhibitors, including INK4 inhibitors (p16, p15, p19, and p18) and Cip/Kip inhibitors (p21, p27, and p53). The cell cycle proteins are of great importance in cancer pathogenesis and prognosis. The p21 impedes the activity of CDK1, CDK2, and CDK4/6 cyclin complexes. This protein serves as a cell cycle regulator and inhibitor at G1 and S phases (104, 105). In an MYC-induced transgenic mouse model of lymphoma, it was observed that lncRNA DANCR was upregulated and promoted cell proliferation in cancer cells via the inhibition of p21 expression. It has been shown that DANCR can play a role in tumorigenic activity. That is why Lu *et al.* (2018) stated that DANCR could be considered a potential target to treat lymphoma (106).

2.13. Bladder carcinoma

Bladder carcinoma (BC), also known as urothelial cell carcinoma (UCC), is the sixth cause of male malignancy and also the most prevalent genital malignancy around the world. The prevalence and mortality rate of BC have increased significantly in the last decade (107-109). There was a significant DANCR upregulation in the BC tissues, compared to the related non-tumor tissues, among BC patients. The expression of DANCR was significantly linked with the TNM stage and histological grade and has an oncogenic role. The DANCR mostly distributes in the cytoplasm and sponges miR-149 to positively control the synthesis of MSI2, resulting in malignant phenotypes in bladder cancer cells (110). Ping *et al.* (2021) explained that DANCR has the main role in the progression and invasion of bladder cancerous cells via the axis of DANCR/miR-335/VEGF (111). Chen *et al.* (2019) revealed that DANCR promotes BC cell proliferation and metastasis through the enhancement of the IL-11-STAT3 signaling pathway and CCND1 transcription level. The expression of cyclin D1 and PLAU increased via stabilizing mRNA, which contains a leucine-rich pentatricopeptide repeat. They also showed the oncogenic influence of DANCR was depressed by treating the cells with an anti-IL-11 antibody or a STAT3 inhibitor (BP-1-102) (112).

2.14. Cervical Cancer

Cervical cancer (CC) is the fourth cause of cancer

death and the third cause of malignancy in women around the world, leading to approximately 300,000 deaths each year (113-115). China Cancer Statistics (2015) reported approximately 100,000 new CC cases and the deaths of 30,000 CC patients (116). Different genetic pathways, such as the DNA base excision repair (APE-1) gene, may contribute to a reduced risk of developing cervix cancer in association with HPV genotypes (117). TGF-β, as a potent cytokine, can modulate or enhance tumor progression by stimulating EMT, cell proliferation, invasion, metastasis, angiogenesis, and the evasion of immune surveillance (118-120). It was reported that TGF-β induces its effect in the later stages of cancer, ultimately leading to tumor progression and metastasis (121). In fact, cancer cells employ a variety of strategies to stop TGF-β as a growth inhibitor and transform its function as an oncogene. TGF-β is able to induce the expression and activation of EGF family cytokines and PDGF in malignant hepatocytes (122, 123). Dysregulated expression of TGF-β signaling has been reported in many cancers, such as hepatocellular carcinoma, colon, prostate, lung, and breast cancers (124, 125). Different studies *in vitro* have demonstrated that increasing EMT is associated with the overexpression of Smad3/4. TGF-β induces important genes involved in ECM via Smads, JNK, p38 MAP-kinase, and TAK1 (TGF-β-activated kinase 1). TAK1 can activate NF-Kb, which transcriptionally promotes MMP-9 synthesis (126, 127).

JNK1 directly enhances the complex formation of Smad3/4, which transcriptionally increases the genes involved in EMT (128). TGF-β-Smad3 signaling increases the expression of Snail1 and Snail2, known as pro-EMT (129-131). DANCR upregulates TGF-βR1 by the regulation of miR-665 and induces CC cell proliferation by targeting it via the ERK/Smad pathway (132). Liang *et al.* (2019) explained that lncRNA DANCR works as a ceRNA to sponge miR-335-5p and increases ROCK1, which is a key regulator of actin-myosin contraction, and is involved in cell motility and stability, and promotes cervical cancer progression and metastasis (133). Hu *et al.* (2021) found the regulatory mechanism of the effect of the lncRNA DANCR on ZEB1 via the working mechanisms of DANCR to sponge miR-145-3p (134).

2.15. Nasopharyngeal carcinoma

Nasopharyngeal carcinoma (NPC) is caused by the malignant transformation of nasopharynx epitheliums (135, 136). Despite combined chemo-radiotherapy, metastasis is the main reason for failure in treatment and death (114, 135-139). It was found that lncRNA DANCR levels are elevated in NPC. The study done by Li *et al.* (2020) demonstrated that increasing DANCR results in increased NPC cell proliferation by binding to the RNA-binding protein 3 (RBM3) protein and stabilizing SOX2 mRNA (140). Wen *et al.* (2018) suggested DANCR as a prognostic biomarker. They found that the stability of HIF-1α mRNA in NPC, via the interaction of DANCR with NF90/NF45, provides suitable circumstances for the progression and metastasis of NPC (141).

2.16. Cholangiocarcinoma

Cholangiocarcinoma (CCA) arises from cholangiocytes (142). The diagnosis of the majority of CCA usually occurs at a late stage, which leads to a median overall survival of less than 12 months, particularly due to a lack of sensitive indicators (143-144). Therefore, finding reliable markers and identifying novel diagnostic and therapeutic targets may be helpful to increase patient survival times. Wang *et al.* (2019) reported that upregulating DANCR could epigenetically cause the progression of CCA through the downregulation of the target tumor suppressor gene FBP1. Therefore, they proposed DANCR as a target for the clinical diagnosis and treatment of CCA (145).

2.17. Esophageal squamous cell carcinoma

Esophageal squamous cell carcinoma (ESCC) is known as one of the most lethal malignancies and a major health burden (146). Despite chemotherapy and radiotherapy, the recurrence of ESCC is frequent and has a poor prognosis with a 20% five-year survival rate (116,147). Bi *et al.* (2020) reported ZNF750 as a mutated driver gene involved in ESCC tumorigenesis and progression. They found that the DANCR/miR-4707-3p/FOXC2 regulatory pathway could affect the ZNF750 level (148).

2.18. Acute myeloid leukemia

Acute myeloid leukemia (AML) is the result of the transformation of hematopoietic stem and/or progenitor cells into aggressive malignant hematopoietic cells (149,150). Cytarabine (Ara-C) and anthracycline are the main agents used in chemotherapeutic approaches against AML (151). Zhang *et al.* (2021) identified DANCR as a novel positive regulator of Ara-C resistance in AML cells, in which enhanced autophagy, through modulating the miR-874-3P/ATG16L1 axis, is the key molecular event that plays an anti-apoptotic role against Ara-C cytotoxicity (152).

3. Evidence Acquisition

This study was conducted on all research articles and reports published since 2000 in Scopus, PubMed, Embase, Google Scholar, and Cochrane databases using keywords such as long non-coding RNA DANCR, long ncRNA DANCR, lncRNA DANCR, and DANCR. The inclusion criteria included being related to the expression and biological mechanism(s) of DANCR in developing tumors in each kind of cancer. In addition, we tried to find the targeted genes by DANCR and relative pathways involved in carcinogenesis in the

base of articles and databases such as deepBase (http://rna.sysu.edu.cn/deepBase/), LNCipedia (https://lncipedia. org/), lncRNAdb (http://lncrna. big.ac.cn/), LncRNAWiki (https://ngdc.cncb.ac.cn/ lncrnawiki1/index.php/Main_Page), LncBook (https://ngdc.cncb.ac.cn/ lncbook/index), lncRNome (http://genome.igib.res.in/lncRNome/), NRED (https://web.archive.org/web/20121128024842/http://nred.matticklab.com/cgi-bin/ncrnadb.pl), C-It-Loci (http://c-it-loci.uni-frankfurt.de/), TANRIC (https://www.tanric.org), and Cancer LncRNA Census (CLC) (https://www.gold-lab.org/clc).

In this study, 166 articles were found with keywords related to lncRNA DANCR in different databases, 121 of which were on the cancer subject, 91 of which were based on cancer in humans. Finally, 76 original articles were selected on expressions and functions. Among them, 28 articles were about the evaluation of the expression of DANCR in various cancers (in vivo studies) and 48 about the mechanism of DANCR action in cancerous cells (in vitro studies). Furthermore, 275 interactions of lncRNA DANCR with microRNAs and mRNAs were found based on bioinformatics (web-based prediction tools). Ultimately, 22 genes and 33 microRNAs were obtained from databases and articles that interplay in carcinogenesis pathways (Diagram 1).

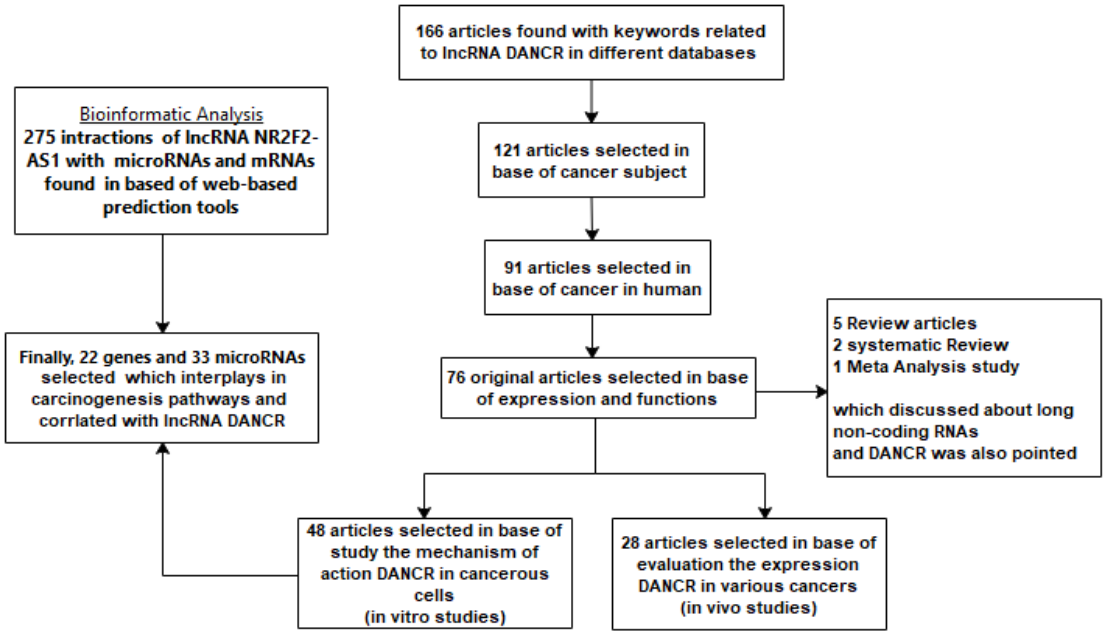

Diagram 1. Strategy of searching the genes targeted by lncRNA DANCR in cancers

Based on our search in databases, there are few review articles on the changes in the expression profile of DANCR, which introduced a few genes under its influence. However, this review article tried not only to collect shreds of evidence regarding the level status of the lncRNA DANCR in various tumors but also comprehensively discussed the molecular mechanisms of this lncRNA in different cellular signaling pathways considering microRNAs, leading to a better understanding of its mode of action to justify why the aberrant expression of DANCR contributes to the pathophysiology of cancer progression and migration. It seems this review article is comparatively pioneering in its own right.

4. Conclusion

DANCR is a cancer-specific ncRNA that contributes significantly to the regulation of genes and microRNAs in different cellular processes, such as proliferation, migration, and invasion in various human cancers. The aberrant expression of the lncRNA DANCR takes place in most of the studied cancers, and it seems to have an oncogenic function, considering the functions of DANCR in various cellular pathways, such as PI3K/Akt, TGF-β, Wnt/Frizzled, JAK-STAT, EMT, and DNA damages. Most studies introduced the lncRNA DANCR as an oncogene, which is able to promote cell proliferation and tumor growth and ultimately turn the condition toward supremacy for the dissemination of cancerous cells and assist in tumor invasion. Although TGF-β promotes apoptosis, cell cycle arrest, and autophagy in tumor cells, it also enhances cell stemness, cell motility, angiogenesis, EMT, and the invasion of tumor cells. The evidence suggested a dual role for TGF-β, as it plays a role as a tumor suppressor in normal cells during the early stages of

tumorigenesis while having an oncogenic function in the later stages of cancer progression (153).

Based on available studies, the regulatory mechanism of DANCR is based on ceRNA. In fact, lncRNA DANCR harbors a number of MREs for various microRNAs involved in different pathways and is consequently able to sequester microRNAs from their targeted mRNAs, which share the same MREs with DANCR. Briefly, lncRNA DANCR mostly exerts its oncogenic role by sponging microRNAs, whose main targets are the mRNAs of different oncogenes involved in cell proliferation, tumor growth, EMT, migration of cancerous cells, and invasion.

This review could declare another molecular mechanism contributing to the pathophysiology of cancer progression, trying to justify why the aberrant expression of DANCR turns the condition toward supremacy for the progression, migration, and invasion of cancerous cells. Therefore, it can be proposed that DANCR can potentially be a candidate as an extremely promising prognostic marker for the early detection of tumor progression and metastasis. DANCR can also be a candidate as a therapeutic target for controlling the progression of several human malignancies.

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Footnotes

Conflicts of Interest: The authors of the current study have no conflicts of interest to declare.

Author Contribution: All authors contributed to the study's conception and design. KM corrected the article, MR and MA performed the literature search and data analysis, MR and MN prepared the draft, and KM critically revised the full original work. All co-authors commented on previous versions of the manuscript. All co-authors read and approved the final manuscript. KM is responsible for the originality of our work and supervised this article

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