Non-coding RNA Research 6 (2021) 29–34

Contents lists available at ScienceDirect

Non-coding RNA Research

journal homepage: www.sciencedirect.com/journal/non-coding-rna-research

# Mechanistic role of DANCR in the choreography of signaling pathways in different cancers: Spotlight on regulation of Wnt/β-catenin and JAK/STAT pathways by oncogenic long non-coding RNA

Ammad Ahmad Farooqi [a,*], Auyezova Ardak Mukhanbetzhanovna [b], Seher Yilmaz [c], Lazzat Karasholakova [d], Ishmuratova Margarita Yulaevna [e]

[a] Institute of Biomedical and Genetic Engineering (IBGE), Islamabad, Pakistan
[b] Department of Healthcare Management, KSPH Kazakhstan Medical University, Almaty, Kazakhstan
[c] Department of Anatomy, Yozgat Bozok University Faculty of Medicine, Yozgat, Turkey
[d] Department of Agronomy and Technical Disciplines, Zhetysu University named after Iliyas Zhansugurov, Str. I.Zhansugurov, 187A, Taldykorgan, 040009, Kazakhstan
[e] E. A. Buketov Karaganda University, Kazakhstan

Buketov University

ARTICLE INFO

*Keywords:*
Long non-coding RNAs
miRNA
Cancer
Apoptosis
Signaling

ABSTRACT

Discovery of non-coding RNAs has paradigmatically shifted our understanding of the multifaceted nature of cancer. It is becoming progressively more understandable that long non-coding RNAs play fundamental role in regulation of cell signaling pathways in different cancers. DANCR has started to gain remarkable appreciation because of its central role in cancer onset and progression. In this review we have attempted to summarize emerging aspects of DANCR-mediated regulation of Wnt/β-catenin and JAK/STAT pathways in different cancers. We have also discussed how DANCR epigenetically inactivated tumor suppressors to promote cancer. There is sufficient experimental evidence related to oncogenic role of DANCR in variety of cancers. However, there is a need to uncover how DANCR modulates various other oncogenic pathways in different cancers.

## 1. Introduction

Long non-coding RNAs (lncRNAs) are untranslated RNAs of >200 nucleotides. LncRNAs have captivated extra-ordinary attention of the basic and molecular oncologists [1–6]. By their size, lncRNAs are discrete from other classes of non-coding RNAs, including piwi-interacting RNAs (piRNAs), microRNAs, small nuclear RNAs and small nucleolar RNAs. Interestingly, lncRNAs have hallmark ability to form secondary and tertiary 3D structures, which depends on characteristically unique Watson-Crick base pairings. These structures enabled lncRNAs to exert protein-like activities, based on spatial conformations and RNA-related functionalities on the basis of nucleic acid complementarity. Advancements in the computational and experimental techniques have enabled us to tackle long-standing questions about the nature and roles of lncRNA functions. LncRNAs have been shown to promote and inhibit cancer progression [7,8].

By sequencing clones obtained from a size-fractionated KG-1 immature myeloid cell line, researchers cloned DANCR, which they designated KIAA0114. The mature transcript is 855 bases long [9,10]. DANCR (Differentiation Antagonizing Non-Protein Coding RNA) has captured notable spotlight because of its ability to promote cancer onset and progression. In this review we have attempted to summarize multidimensional role of DANCR in cancer progression via regulation of JAK/STAT and Wnt/β-catenin signaling in different cancers. We will also analyze how DANCR epigenetically inactivates tumor suppressors to promote cancer and how DANCR behaves as a miRNA sponge to potentiate the expression of oncogenes.

## 2. DANCR-mediated regulation of JAK/STAT signaling

JAK/STAT pathway transmitted information intracellularly for regulation of myriad of cellular activities. JAK family of kinases has the ability to phosphorylate substrate proteins called STATs (signal transducer and activator of transcription) [11]. These phosphorylated STAT molecules translocate into the nucleus and control transcription of target gene networks [12]. In this section we will focus on the interplay between JAK/STAT and DANCR.

DANCR activated IL-11-STAT3-driven transduction cascade to

* Corresponding author.
*E-mail address:* Farooqiammadahmad@gmail.com (A.A. Farooqi).

https://doi.org/10.1016/j.ncrna.2021.01.001
Received 2 December 2020; Received in revised form 2 January 2021; Accepted 7 January 2021
Available online 13 January 2021
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promote bladder cancer metastasis [13]. Levels of p-JAK2 and p-STAT3 were noted to be reduced in DANCR-knockdown cells. Importantly, anti-IL-11 antibody reduced the levels of p-JAK2 and p-STAT3. LRPPRC (Leucine-rich pentatricopeptide repeat containing) has the ability to stabilize mRNA (Fig. 1). LRPPRC knockdown considerably abrogated DANCR-induced increase in the mRNA and protein levels of target genes in bladder cancer cells. Notably, knockdown of LRPPRC or DANCR resulted in significant reduction in the half-lives of CCND1 and PLAU mRNAs in bladder cancer cells, however DANCR overexpression increased their half-lives. Fragment of the nucleotides stretching from 350 to 670 in the DANCR transcript has critical roles. These fragments formed a stem-loop structure and interacted with LRPPRC. Protein levels of CCND1 and PLAU were remarkably reduced in the DANCR-silenced xenografted tumors, but there was a marked increase in the levels of CCND1 and PLAU in the tumor tissues of the mice inoculated with DANCR-overexpressing bladder cancer cells [13].

DANCR promoted activation of STAT3 by promoting the interaction between JAK1 and STAT3 (Fig. 1) [14]. DANCR specifically interacted with STAT3 and intriguingly, IL-6 treatment further increased the interaction between DANCR and STAT3. Furthermore, IL-6 promoted the co-localization of STAT3 and DANCR in cytoplasm. IL-6 significantly induced STAT3 phosphorylation, while DANCR knockdown notably abrogated IL-6 induced STAT3 phosphorylation in both 5–8F and HNE2 cells. Moreover, DANCR knockdown inhibited STAT3-mediated transcriptional upregulation of c-myc and survivin. DANCR knockdown evidently reduced nuclear accumulation of p-STAT3 [14].

PSMD10 (Proteasome 26S subunit, Non-ATPase 10) activated IL-6/STAT3 signaling in HCC cells [15]. DANCR blocked miRNA-induced targeting of PSMD10 via binding to 3′UTR of PSMD10. DANCR overexpression increased the p-STAT3 levels, which was abolished by knockdown of PSMD10 in Hep3B and Huh7 cells. IL-6 elevated both DANCR and PSMD10 levels in Hep3B and Huh7 cells. Conversely, DANCR and PSMD10 transcription was repressed by STAT3 inhibitors [15]. Therefore, collectively, these findings suggested that STAT3-mediated transcriptional upregulation of DANCR in HCC cells. DANCR potentiated the expression of PSMD10 by blocking miRNA-induced targeting of PSMD10. Consequently, PSMD10 promoted JAK/STAT-driven downstream signaling and drug resistance.

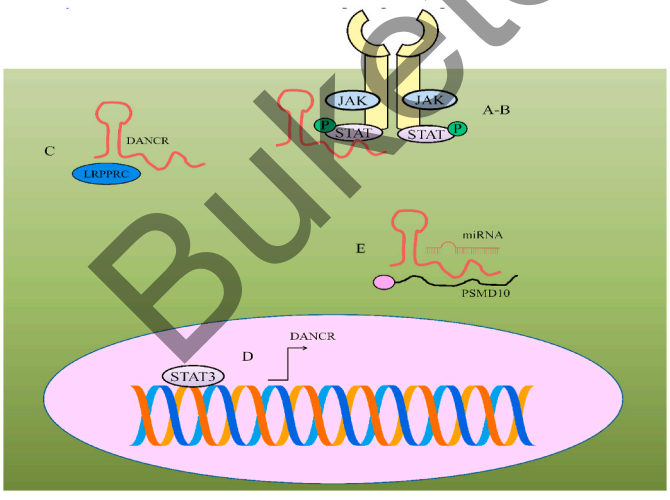


**Fig. 1.** Shows (A–B) interplay between DANCR and JAK/STAT signaling. DANCR promoted the interaction between JAK and STAT and potentiated JAK-mediated STAT signaling. (C) LRPPRC (Leucine-rich pentatricopeptide repeat containing) has the ability to stabilize mRNA. DANCR interacted with LRPPRC and enhanced the stability of target mRNAs. (D–E) STAT3 transcriptionally upregulated DANCR. DANCR interfered with miRNA-mediated targeting of PSMD10.

## 3. Wnt/β-catenin signaling

Wnt-induced receptor activation can transduce the signals intracellularly through discrete pathways that are categorized into canonical and non-canonical Wnt signaling routes. In this section we will exclusively focus on the β-catenin-dependent pathway that is linked to the cancer progression. We will also summarize how DANCR potentiate Wnt/β-catenin signaling in different cancers.

In the absence of WNT ligands, cytosolic β-catenin is degraded continuously by a destruction complex consisting of oligomerizing scaffold proteins APC (adenomatous polyposis coli), Axin, casein kinase and glycogen synthase kinase 3β (GSK-3β) [16]. These kinases phosphorylated β-catenin and tagged it for ubiquitylation subsequent proteasomal degradation. Activation of Wnt/β-catenin signaling resulted in the nuclear accumulation of β-catenin and transcriptional modulation of myriad of target genes [17–19].

SALL4 (SAL-Like 4) transcriptionally upregulated DANCR in MGC-803 cells [20]. DANCR overexpression increased the levels of β-catenin in gastric cancer cells. Overall, the findings clearly indicated that SALL4-induced DANCR promoted Wnt/β-catenin signaling in gastric cancer cells [20].

In another study it was shown that DANCR effectively blocked targeting of β-catenin by miR-214 and miR-320a in HCC cells [21]. Systemic delivery of DANCR interference sequence through injection induced reduction in the number and size of intrahepatic tumor loci in experimental mice [21].

FRAT1 and FRAT2 (Frequently rearranged in advanced T-cell lymphomas) positively regulated Wnt/β-catenin signaling [22]. DANCR overexpression induced upregulation of mRNA and protein levels of FRAT1 and FRAT2. Interestingly, FRAT1 and FRAT2 not only inhibited GSK3-mediated β-catenin phosphorylation and degradation but also facilitated nuclear shuttling of β-catenin for transcriptional modulation of target gene network [23,24]. Likewise, DANCR overexpression increased the levels of nuclear β-catenin, while DANCR knockdown lowered nuclear β-catenin levels in cervical cancer cells [22]. Overview of these findings clearly supported the fact that DANCR promoted Wnt/β-catenin signaling by stabilization of β-catenin and enhancing its accumulation in the nucleus.

DANCR contains miRNA recognition elements for miR-216a. miR-26a exerted tumor suppressive effects but DANCR interfered with miR-26a-mediated inhibition of Wnt/β-catenin signaling [25].

## 4. Epigenetic inactivation of tumor suppressor genes

PRC2 (Polycomb repressive complex-2) activity is dependent on the EZH1 and EZH2, which deposit methylation states on lysine 27 of histone H3 (H3K27). Studies have shown that EZH1 and EZH2 have unique enzymatic properties and are mutually exclusive within PRC2. Interestingly, under the same reaction conditions, EZH2 has been shown to demonstrate higher methyltransferase activity [26]. Recent breakthroughs in the biology of PRC2 have expanded our perspectives on its regulation and functions, and uncovered a role for lncRNAs in the recruitment of PRC2 to target genes. There was an evident increase in the levels of H3K27me3 in DANCR-overexpressing cancer cells (Fig. 2). DANCR has been shown to work synchronously with EZH2 to epigenetically inactivate tumor suppressors in wide variety of cancers.

DANCR effectively downregulated SOCS3(Suppressor of cytokine signaling-3) in breast cancer cells. SOCS3 overexpression efficiently prevented multiple malignant phenotypes induced by DANCR in both MCF7 and MCF10A cells [27].

Fructose-1, 6-biphosphatase (FBP1) has also been shown to be epigenetically silenced by DANCR in cholangiocarcinoma cells [28]. DANCR and FBP1 overexpressing HuCCT1 cells were injected into the mice to analyze tumor growth development. FBP1 partially reversed DANCR-induced tumor growth in xenografted mice [28].

TIMPs (Tissue Inhibitor of Metalloproteinases) have the ability to

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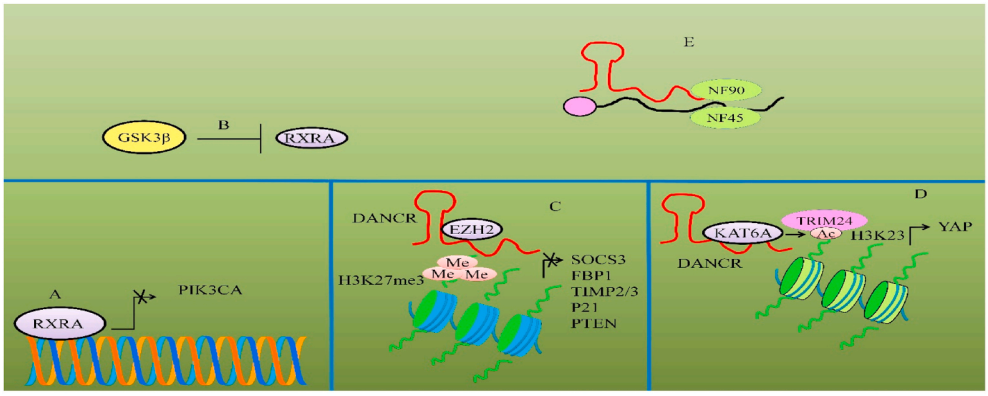


**Fig. 2.** Shows (A–B) GSK3β-mediated inactivation of RXRA. RXRA transcriptionally repressed PIK3CA. However, GSK3β-mediated inactivation of RXRA caused an increase in PIK3CA. (C) DANCR worked synchronously with EZH2 and epigenetically inactivated different tumor suppressor genes. Whereas, DANCR stimulated the expression of YAP. (D) DANCR worked jointly with KAT6A and promoted KAT6A-mediated acetylation of H3K23. Acetylated-H3K23 served as a platform for the TRIM protein which stimulated YAP expression. (E) DANCR stabilized oncogenic mRNA transcripts.

control diverse metalloproteinases. TIMP2/3 was epigenetically silenced by DANCR and EZH2 in prostate cancer cells [29]. Pulmonary metastatic foci were noted to be reduced in mice xenografted with DANCR-silenced CW22Rv1 prostate cancer cells. DANCR knockdown induced an increase in the levels of TIMP2/3 in the metastatic foci of mice inoculated with DANCR-silenced CW22Rv1 cancer cells [29].

DANCR knockdown reduced the levels of EZH2 binding to the promoter of p21 and H3K27me3 levels in promoter region of p21 gene [30].

DANCR worked with EZH2 and epigenetically inactivated PTEN [31]. Resveratrol markedly suppressed tumor growth in mice xenografted with SUNE-1 cells. DANCR levels were noted to be reduced in the tumor tissues after resveratrol treatment. Immunohistochemical assays clearly indicated that resveratrol increased the expression of PTEN in tumor tissues [31].

## 5. Mechanistic regulation of oncogenic protein networks by DANCR

RNA has been reported to undergo biochemical modifications. Accordingly, N6-methyladenosine (m6A) modification has a central roleplay. IGF2BPs (Insulin-like growth factor binding proteins) function as a discrete family of m6A readers having unique ability to recognize myriad of mRNA transcripts. These readers increased the stability of target mRNAs in an m6A-dependent manner [32]. DANCR is methylated at m6A and IGF2BP2 acts as a reader for the methylated DANCR to enhance its stability. Growth of the tumors was markedly reduced in mice xenografted with DANCR-silenced BXPC-3 cells. More importantly, tumor growth was also found to be significantly reduced in mice orthotopically injected with DANCR-silenced BXPC-3 cells directly into the pancreas [32].

TRIM24 is a histone reader and belongs to TRIM/RBCC family of proteins [33]. KAT6A (lysine acetyltransferase 6A) induced acetylation of H3K23 and potentiated binding of TRIM24 to H3K23ac. DANCR and KAT6A worked synchronously and promoted TRIM24-mediated transcriptional upregulation of YAP in colorectal cancer cells (Fig. 2) [33].

DANCR binds to NF90 and NF45 to stabilize different proteins in cancer cells [34]. Importantly, levels of HIF-1α were noted to be reduced in DANCR-knockdown SUNE1 and HONE1 cells. Degradation of HIF-1α mRNA was notable in DANCR knockdown cancer cells. DANCR interacted with NF90/NF45 and stabilized HIF-1α mRNA. There was a marked reduction in HIF-1α expression in SUNE1 and HONE1 cells after knockdown of NF90 or NF45 under hypoxic conditions [34].

PIK3CA gene encodes the PIK3 catalytic subunit isoform p110α. RXRA (Retinoid X Receptor, alpha) acted as a repressor and transcriptionally downregulated PIK3CA [35]. GSK3β-mediated phosphorylation of RXRA had been shown to inactivate it. DANCR facilitated GSK3β-mediated phosphorylation of RXRA and stimulated PIK3CA expression in triple negative breast cancer cells (Fig. 2). Consequently, DANCR induced expression of PIK3CA and activated PI3K/AKT pathway [35].

SP1 transcriptionally upregulated DANCR in ovarian cancer tissues and cells (SKOV3, CAOV3 and A2780). DANCR inhibition caused suppression of cell migration and invasion of CAOV3. Whereas, DANCR overexpression contributed to growth of SKOV3 cells [36].

## 6. Sponge effects of DANCR

Our understanding of the interplay among DANCR, miRNAs and regulatory networks has improved remarkably in the past few years (shown in Fig. 3).

## 7. MMPs

MMPs (Matrix metalloproteinases) have outgrown the field of extracellular-matrix biology and have progressed towards being central and multifaceted regulators in molecular oncology.

There is sufficient evidence of complementary pair binding between DANCR and miRNAs. MMP16 and DANCR contain the same binding site for miRNA-33b. DANCR blocked miR-33b-mediated targeting of MMP16 in SW1990 and PANC-1 cells [37].

Tumor growths were noted to be significantly enhanced in mice inoculated with CAL-27 or TCa-8113 cells.

Whereas, tumor growth was noted to be reduced in mice xenografted with DANCR-silenced cancer cells. Expression levels of MMP2 and MMP9 were reduced in tumor tissues. KLF8 (Kruppel-like Factor 8) is another oncogene promoted by DANCR. DANCR interfered with miR-135a-5p-mediated inhibition of KLF8. DANCR potentiated the expression of MMPs and KLF8 to promote the growth of tongue squamous cell carcinoma cells [38].

miR-613 and miR-34c contain matching sequences with DANCR at 3′-UTR. miR-613 and miR-34c directly targeted MMP9 in retinoblastoma cells. DANCR acted as a sponge and sequestered away miR-613 and miR-34c [39].

## 8. JAG1

DANCR knockdown induced an increase in docetaxel sensitivity in drug-resistant prostate cancer cells. Jagged1 (JAG1) is a cell surface ligand that primarily functions in the highly conserved Notch signaling cascade. JAG1 knockdown enhanced the docetaxel sensitivity in drug-resistant prostate cancer cells. JAG1 was direct target of miR-34a-5p. DANCR promoted drug resistance in prostate cancer cells by interfering with miR-34a-5p-mediated targeting of JAG1 [40].

## 9. AXL

AXL is a receptor tyrosine kinase reportedly involved in the activation of PI3K/Akt/NFκB transduction cascade. DANCR promoted

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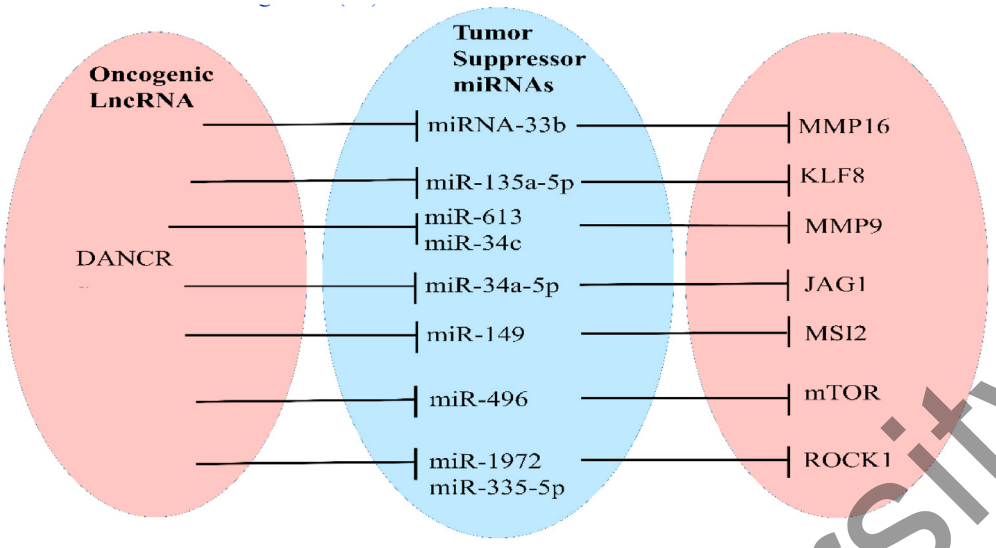


**Fig. 3.** Provides summary of DANCR-mediated targeting of tumor suppressor miRNAs to promote cancer.

cisplatin resistance via activation of AXL/PI3K/Akt/NFκB signaling cascade in glioma cells. miR-1-3p, miR-33a-5p, miR-33b-5p, miR-206 and miR-613 have the ability to target AXL in glioma cells. However, DANCR blocked miRNA-mediated targeting of AXL [41].

### 10. Musashi RNA binding protein 2 (MSI2)

DANCR sequestered miR-149 away from MSI2 and promoted its expression in bladder cancer cells [42]. DANCR knockdown induced an increase in the levels of E-cadherin and reduced N-cadherin in bladder cancer cells. Tumor growth and metastases were significantly reduced in mice xenografted with DANCR-silenced bladder cancer cells [42].

### 11. Mechanistic target of Rapamycin (mTOR)

mTOR played central role in cancer metastasis and invasion. miR-496 acted as a tumor suppressor but DANCR interfered with miR-496-mediated targeting of mTOR [43]. Tumor volumes were noted to be much smaller in mice inoculated with DANCR-silenced A549 cells [43].

### 12. VEGF

DANCR promoted tumor growth and angiogenesis in ovarian cancer cells. DANCR acted as a molecular sponge and efficiently blocked miR-145-mediated targeting of VEGF [44].

### 13. ROCK1

ROCK1 (Rho associated coiled-coil containing protein kinase 1) played instrumental role in migration and invasion of cervical cancer cells (**45**). miR-335-5p served as a tumor suppressor miRNA and directly targeted ROCK1. However, DANCR interfered with miR-335-5p-mediated targeting of ROCK1 in cervical cancer cells [45]. ROCK1 potently promoted metastatic spread of cancer cells. miR-1972 and miR-335-5p negatively regulated ROCK1 in osteosarcoma cells [46]. However, DANCR blocked miR-1972 and miR-335-5p-mediated targeting of ROCK1. Pulmonary metastatic nodules were noted in mice inoculated with DANCR-overexpressing 143B cells [46].

### 14. FOXC2

ZNF750 (Zinc Finger protein 750) acted as a tumor suppressor and transcriptionally downregulated DANCR in esophageal squamous cell carcinoma cells (**47**). However, DANCR was noted to be upregulated in ZNF750-depleted cancer cells. DANCR promoted FOXC2-driven signaling by interfering with miR-4707-3p-mediated targeting of FOXC2 [47].

### 15. Kruppel-like factor 12 (KLF12)

Kruppel-like factor 12 (KLF12) played critical role in HCC progression [48]. DANCR interfered with miR-216a-5p-mediated targeting of KLF12. Tumor growth was considerably reduced in mice xenografted with DANCR-silenced HepG2 cells. KLF12 was notably reduced but the levels of miR-216a-5p were found to be enhanced in xenografted mice [48].

### 16. LIMK1/Cofilin1 pathway

Cofilin is an important actin-binding protein critical for regulation of the actin polymerization within the cells. LIMK1 is a serine/threonine kinase mainly involved in the regulation of actin polymerization via phosphorylation and inactivation of the cofilin [49]. Pulmonary metastatic nodules were noted to be reduced in mice injected with DANCR-silenced SMMC-7721 cells. miR-27a-3p mimics potently blocked clonal formation and migration of HCC cells. DANCR interfered with miR-27a-3p-mediated targeting of LIMK1 and enhanced migratory and invasive potential of HCC cells [49].

### 17. SRY-box proteins (SOX)

TUFT1 elevated the expression of DANCR in MDA-MB-231 cells [50]. DANCR sequestered miR-874-3p away and potentiated the expression of SOX2. miR-874-3p overexpression induced significant reduction in the levels of SOX2 in MDA-MB-468 and MDA-MB-231 cells. E-cadherin levels were reduced in breast cancer cells transfected with SOX2. There was a marked reduction in tumor growth in mice xenografted with DANCR-silenced MDA-MB-231 cells. However, the growth inhibitory effects were more pronounced in mice inoculated with DANCR-silenced and miR-874-3p-transfected MDA-MB-231 cells [50].

miR-216a-5p negatively regulated SOX5 in osteosarcoma cells [51]. DANCR blocked miR-216a-5p-mediated targeting of SOX5. Tumor regression was markedly enhanced in mice xenografted with DANCR-silenced 143B cells. More importantly, miR-216a-5p was noted to be upregulated but levels of SOX5 were found to be downregulated in xenografted mice [51].

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## 18. NLRP3

Levels of N-cadherin and NLRP3 were found to be reduced in DANCR-silenced MIA PaCa-2 and BxPC-3 pancreatic cancer cells. Tumor growth was notably reduced in mice inoculated with DANCR-silenced MIA PaCa-2 cancer cells. miR-135a-5p expression was higher in tumors tissues of the mice injected DANCR-silenced MIA PaCa-2 cancer cells. Expression levels of NLRP3 and Ki67 were also noted to be reduced in tumor-bearing mice [52].

## 19. Concluding remarks

LncRNAs are new players that will shape future research in molecular oncology. Given their linchpin role in multiple oncogenic mechanisms, the study of lncRNAs will be the key to enhance our knowledge of cancer biology and to classify tumors. DANCR has been shown to promote different oncogenic signaling pathways. Additionally, DANCR epigenetically inactivated wide-variety of tumor suppressors to promote cancer. However, there are unanswered questions related to broader role of DANCR in regulation of sonic hedgehog pathway and Notch-driven oncogenic cascade in different cancers. Interplay between DANCR and TRAIL-mediated apoptotic pathway has also not been deeply investigated. Answers to these questions will help the researchers to answer the bigger question of complicated regulatory roles of DANCR in different cancers.

## Declaration of competing interest

I declare on the behalf of all authors that none of the authors have any conflict of interest.

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