

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

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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

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promote bladder cancer metastasis [13]. Levels of p-JAK2 and p-STAT3 were noted to be reduced in DANCER-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 DANCER-induced increase in the mRNA and protein levels of target genes in bladder cancer cells. Notably, knockdown of LRPPRC or DANCER resulted in significant reduction in the half-lives of CCND1 and PLAU mRNAs in bladder cancer cells, however DANCER overexpression increased their half-lives. Fragment of the nucleotides stretching from 350 to 670 in the DANCER 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 DANCER-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 DANCER-overexpressing bladder cancer cells [13].

DANCER promoted activation of STAT3 by promoting the interaction between JAK1 and STAT3 (Fig. 1) [14]. DANCER specifically interacted with STAT3 and intriguingly, IL-6 treatment further increased the interaction between DANCER and STAT3. Furthermore, IL-6 promoted the co-localization of STAT3 and DANCER in cytoplasm. IL-6 significantly induced STAT3 phosphorylation, while DANCER knockdown notably abrogated IL-6 induced STAT3 phosphorylation in both 5–8F and HNE2 cells. Moreover, DANCER knockdown inhibited STAT3-mediated transcriptional upregulation of c-myc and survivin. DANCER 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]. DANCER blocked miRNA-induced targeting of PSMD10 via binding to 3'UTR of PSMD10. DANCER overexpression increased the p-STAT3 levels, which was abolished by knockdown of PSMD10 in Hep3B and Huh7 cells. IL-6 elevated both DANCER and PSMD10 levels in Hep3B and Huh7 cells. Conversely, DANCER and PSMD10 transcription was repressed by STAT3 inhibitors [15]. Therefore, collectively, these findings suggested that STAT3-mediated transcriptional upregulation of DANCER in HCC cells. DANCER potentiated the expression of PSMD10 by blocking miRNA-induced targeting of PSMD10. Consequently, PSMD10 promoted JAK/STAT-driven downstream signaling and drug resistance.

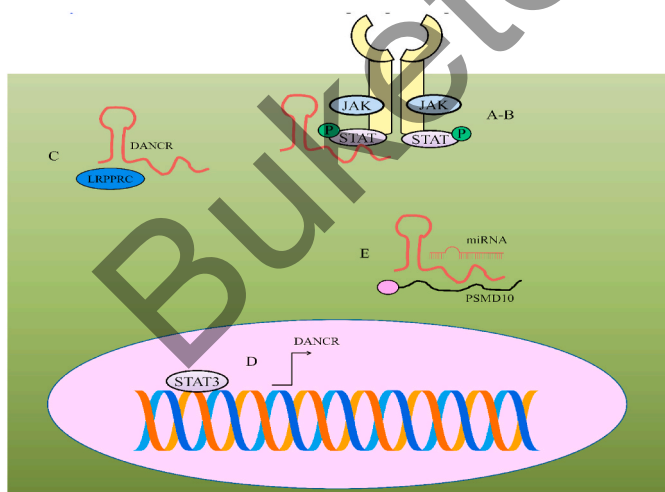


Fig. 1. Shows (A–B) interplay between DANCER and JAK/STAT signaling. DANCER promoted the interaction between JAK and STAT and potentiated JAK-mediated STAT signaling. (C) LRPPRC (Leucine-rich pentatricopeptide repeat containing) has the ability to stabilize mRNA. DANCER interacted with LRPPRC and enhanced the stability of target mRNAs. (D–E) STAT3 transcriptionally upregulated DANCER. DANCER 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 DANCER 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 3 β (GSK-3 β) [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 DANCER in MGC-803 cells [20]. DANCER overexpression increased the levels of β -catenin in gastric cancer cells. Overall, the findings clearly indicated that SALL4-induced DANCER promoted Wnt/ β -catenin signaling in gastric cancer cells [20].

In another study it was shown that DANCER effectively blocked targeting of β -catenin by miR-214 and miR-320a in HCC cells [21]. Systemic delivery of DANCER 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]. DANCER 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, DANCER overexpression increased the levels of nuclear β -catenin, while DANCER knockdown lowered nuclear β -catenin levels in cervical cancer cells [22]. Overview of these findings clearly supported the fact that DANCER promoted Wnt/ β -catenin signaling by stabilization of β -catenin and enhancing its accumulation in the nucleus.

DANCER contains miRNA recognition elements for miR-216a. miR-26a exerted tumor suppressive effects but DANCER 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 DANCER-overexpressing cancer cells (Fig. 2). DANCER has been shown to work synchronously with EZH2 to epigenetically inactivate tumor suppressors in wide variety of cancers.

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

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

TIMPs (Tissue Inhibitor of Metalloproteinases) have the ability to

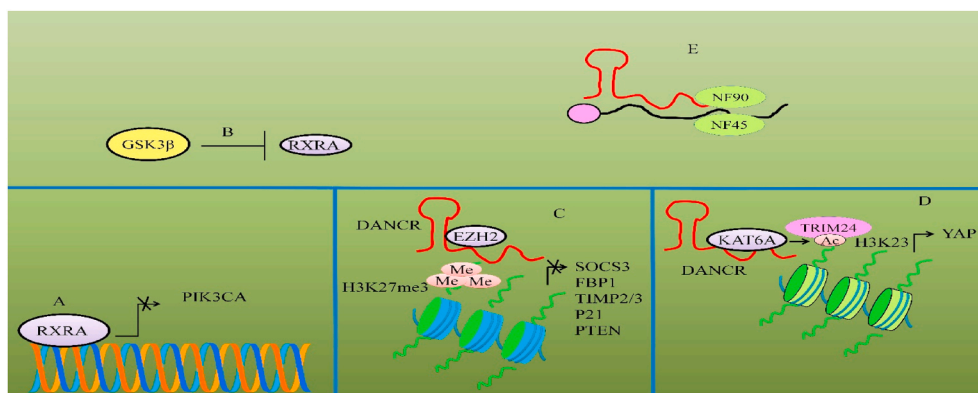


Fig. 2. Shows (A–B) GSK3 β -mediated inactivation of RXRA. RXRA transcriptionally repressed PIK3CA. However, GSK3 β -mediated inactivation of RXRA caused an increase in PIK3CA. (C) DANCR worked synchronously with EZH2 and epigenetically inactivated different tumor suppressor genes. Whereas, DANCR stimulated 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-1 α were noted to be reduced in DANCR-knockdown SUNE1 and HONE1 cells. Degradation of HIF-1 α mRNA was notable in DANCR knockdown cancer cells. DANCR interacted with NF90/NF45 and stabilized HIF-1 α mRNA. There was a marked reduction in HIF-1 α expression in SUNE1 and HONE1 cells after knockdown of NF90 or NF45 under hypoxic conditions [34].

PIK3CA gene encodes the PIK3 catalytic subunit isoform p110 α . RXRA (Retinoid X Receptor, alpha) acted as a repressor and transcriptionally downregulated PIK3CA [35]. GSK3 β -mediated phosphorylation of RXRA had been shown to inactivate it. DANCR facilitated GSK3 β -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/NF κ B transduction cascade. DANCR promoted

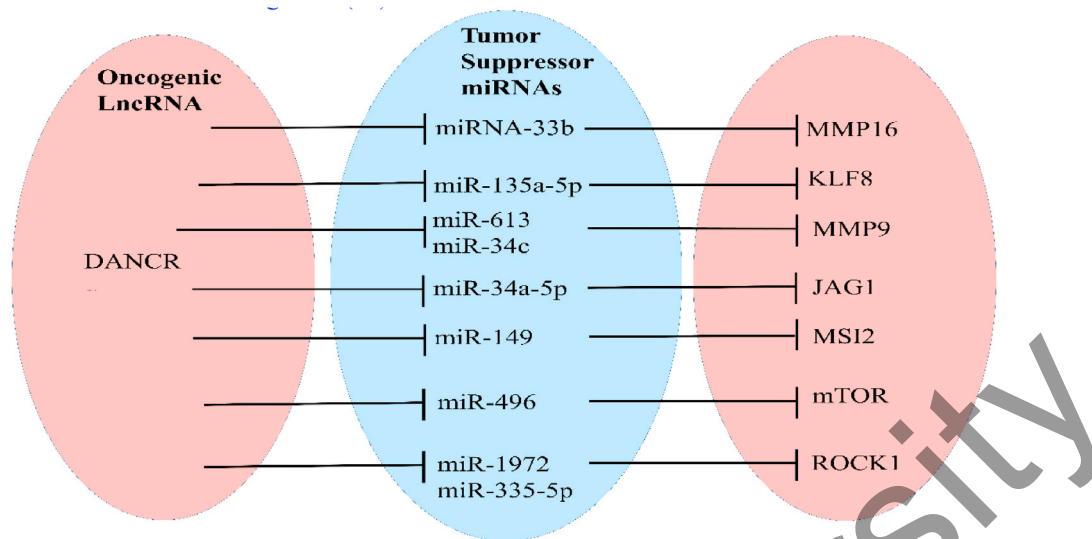


Fig. 3. Provides summary of DANCER-mediated targeting of tumor suppressor miRNAs to promote cancer.

cisplatin resistance via activation of AXL/PI3K/Akt/NF κ B 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, DANCER blocked miRNA-mediated targeting of AXL [41].

10. Musashi RNA binding protein 2 (MSI2)

DANCER sequestered miR-149 away from MSI2 and promoted its expression in bladder cancer cells [42]. DANCER 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 DANCER-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 DANCER interfered with miR-496-mediated targeting of mTOR [43]. Tumor volumes were noted to be much smaller in mice inoculated with DANCER-silenced A549 cells [43].

12. VEGF

DANCER promoted tumor growth and angiogenesis in ovarian cancer cells. DANCER 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, DANCER 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, DANCER blocked miR-1972 and miR-335-5p-mediated targeting of ROCK1. Pulmonary metastatic nodules were noted in mice inoculated with DANCER-overexpressing 143B cells [46].

14. FOXC2

ZNF750 (Zinc Finger protein 750) acted as a tumor suppressor and transcriptionally downregulated DANCER in esophageal squamous cell

carcinoma cells (47). However, DANCER was noted to be upregulated in ZNF750-depleted cancer cells. DANCER 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]. DANCER interfered with miR-216a-5p-mediated targeting of KLF12. Tumor growth was considerably reduced in mice xenografted with DANCER-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 DANCER-silenced SMMC-7721 cells. miR-27a-3p mimics potently blocked clonal formation and migration of HCC cells. DANCER 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 DANCER in MDA-MB-231 cells [50]. DANCER 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 DANCER-silenced MDA-MB-231 cells. However, the growth inhibitory effects were more pronounced in mice inoculated with DANCER-silenced and miR-874-3p-transfected MDA-MB-231 cells [50].

miR-216a-5p negatively regulated SOX5 in osteosarcoma cells [51]. DANCER blocked miR-216a-5p-mediated targeting of SOX5. Tumor regression was markedly enhanced in mice xenografted with DANCER-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].

18. NLRP3

Levels of N-cadherin and NLRP3 were found to be reduced in DANCER-silenced MIA PaCa-2 and BxPC-3 pancreatic cancer cells. Tumor growth was notably reduced in mice inoculated with DANCER-silenced MIA PaCa-2 cancer cells. miR-135a-5p expression was higher in tumors tissues of the mice injected DANCER-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. DANCER has been shown to promote different oncogenic signaling pathways. Additionally, DANCER epigenetically inactivated wide-variety of tumor suppressors to promote cancer. However, there are unanswered questions related to broader role of DANCER in regulation of sonic hedgehog pathway and Notch-driven oncogenic cascade in different cancers. Interplay between DANCER 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 DANCER 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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