A review on the role of DANCR in the carcinogenesis

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Abstract
DANCR is an RNA gene located on chr4. This gene has several splice variants. Up-regulation of DANCR has been reported in many types of cancers. This IncRNA is mainly located in the cytoplasm and regulates genes expression at post-transcriptional level. In fact, it acts as a molecular sponge for a variety of miRNAs, including miR-874-3p, miR-335, miR-149, miR-4319, miR-758-3p, miR-216a-5p, miR-874-3p, miR-33a-5p, miR-335-5p, miR-145-3p, miR-665, miR-345-5p and miR-125b-5p. DANCR also regulates activity of PI3K/AKT/NF-κB, Wnt/β-catenin, ERK/MAPK, IL-6/JAK1/STAT3, Smad2/3, p53, FAK/PI3K/AKT/GSK3β/Snail pathways. In the current narrative review article, we summarize the roles of DANCR in the carcinogenesis, with an especial emphasis on its role in the development of osteosarcoma and lung, liver, pancreatic and colorectal cancers.

Keywords: DANCR, IncRNA, Cancer

Introduction
DANCR (Differentiation Antagonizing Non-Protein Coding RNA) is an RNA gene located on chr4: 52,712,257–52,723,623, plus strand. It has a size of 11,367 bases. This gene has 14 splice variants with sizes ranging from 272 bp (DANCR-207) to 6065 bp (DANCR-203), all of them being categorized as long non-coding RNA (lncRNA). This lncRNA has been regarded as a cancer-associated lncRNA, since its up-regulation has been reported in several cancer types in association with enhancement of cell proliferation and malignant properties [1]. DANCR regulates gene expression at post-transcriptional level [1]. Based on the findings obtained from RNA fluorescence in situ hybridization and expression assays in the cellular fractions, DANCR has been found to be primarily located in the cytoplasm [2]. In the current narrative review article, we summarize the roles of DANCR in the carcinogenesis, with an especial emphasis on its role in the development of osteosarcoma and lung, liver, pancreatic and colorectal cancers.

Cell line studies
Up-regulation of DANCR has been shown to upsurge proliferation, migratory propensity, and invasiveness of osteosarcoma cells. From a functional aspect, DANCR promotes progression of osteosarcoma through induction of cancer stem cells properties. DANCR up-regulates expression of AXL through sequestering miR-33a-5p. Further, DANCR enhances activity of AXL/Akt pathway. Cumulatively, DANCR is an important regulator of osteosarcoma progression [2]. Another study in osteosarcoma cells has indicated that inhibition of DANCR leads to decrease in ROCK1-mediated proliferation and metastasis. Mechanistically, DANCR regulates expression of ROCK1 through sequestering miR-335-5p and miR-1972 [3]. Other studies have revealed the impacts of DANCR/miR-149/MSI2 axis [4] and DANCR/miR-216a-5p/SOX5 [5] axes in the pathoetiology of osteosarcoma. Moreover,
METTL3 has been shown to contribute in this type of cancer through enhancement of stability of DANCR transcripts through m6A modification [6].

In bladder cancer cells, DANCR silencing has inhibited proliferation, migratory potential and invasion. DANCR has been shown to target miR-335/VEGF-C. miR-335 mimics could promote proliferation and invasive properties bladder cancer cells. In contrast, up-regulation of DANCR removes the effect of miR-335 mimics on these cells [7]. In addition, DANCR enhances metastatic and proliferative abilities of bladder cancer cells through increasing IL-11-STAT3 signals and CCND1 levels [8]. Finally, miR-149/MSI2 has been identified as another route of participation of DANCR in progression of bladder cancer [9].

In lung cancer cells, DANCR expression levels have been negatively correlated with levels of miR-216a [10]. Another study has identified the impact of DANCR/miR-1225-3p/ErbB2 axis in the regulation of metastasis of lung cancer cells [11]. Moreover, DANCR participates in the progression of this type of cancer through sequestering miR-496 and further modulating expression of mTOR [12]. DANCR can also regulate miR-214-5p/CIZ1 axis [13]. Moreover, invasive properties of lung cancer cells are regulated by DANCR through suppression of miR-216 and subsequent activation of Wnt/β-Catenin signals [14]. Figure 1 shows roles of DANCR in osteosarcoma, lung cancer, liver cancer, colorectal cancer, bladder cancer, and pancreatic cancer.
Hepatocellular carcinoma is another type of cancer in which DANCR has an important effect. Up-regulation of DANCR in these cells has been associated with down-regulation of miR-125b-5p. DANCR silencing or miR-125b-5p mimics could reduce cell cycle progression in HepG2 or Huh-7 cells, while promoting cell apoptosis. Both interventions could also inhibit migratory potential and invasiveness of these cells. Mechanistically, DANCR facilitates progression of this cancer through sponging miR-125b-5p and activating MAPK pathway [15].

DANCR could also contribute to the liver carcinogenesis through sponging miR-216a-5p and surging expression of KLF12 [16]. Another study in hepatocellular carcinoma cells has shown over-expression of DANCR and ATG7, and down-regulation of miR-222-3p. Besides, DANCR silencing has intimidated proliferation and autophagy of these cells. Mechanistically, DANCR induces proliferation, colony construction and autophagy of these cells through enhancing expression of ATG7 and decreasing expression of miR-222-3p [17]. Notably, DANCR can also affect response of hepatocellular carcinoma cells to sorafenib through enhancing activity of IL-6/STAT3 signals [18]. This lncRNA can also affect stemness and epithelial–mesenchymal transition (EMT) through modulating expression of CTNNB1 [19] and regulation of activity of ROCK1/LIMK1/COFILIN1 pathway [20], respectively.

In colorectal cancer cells, DANCR has been shown to affect activity of miR-125b-5p/HK2 axis to induce resistance to cisplatin through induction of anaerobic glycolysis [21]. In addition, DANCR/miR-518a-3p/MDMA axis has been identified as an imperative regulator of growth and malignant behavior of these malignant cells [22]. Most notably, the interaction between DANCR and the important oncogenic lncRNA MALAT1 has been found to induce resistance to doxorubicin-associated apoptosis in colorectal cancer cells [23].

In pancreatic cancer cells, DANCR regulates expression of miR-33b to promote proliferation and metastatic abilities [24]. Moreover, the invasive properties of these cells are regulated by DANCR/miR-214-5p/E2F2 [25] and DANCR/miR-135a/NLRP37 [26] axes. Figure 1 shows oncogenic roles of DANCR in osteosarcoma, lung cancer, liver cancer, colorectal cancer, bladder cancer, and pancreatic cancer. Expression of DANCR has been found to be increased in triple negative breast cancer cell lines. Notably, DANCR silencing has led to suppression of proliferation of these cells. Functional studies have detected that DANCR binding with RXRA enhances phosphorylation of this protein on its serine 49/78 via GSK3β, which subsequently leads to activation of PIK3CA transcription, and induction of PI3K/AKT signals [27]. Another study has shown over-expression of DANCR and VAPB in breast cancer cells, parallel with down-regulation of miR-4319. DANCR silencing not only has stalled proliferation, migratory potential, and invasiveness of breast cancer cells, but also has induced their apoptosis. These effects have been found to be mediated through regulation of miR-4319. This study has revealed the importance of DANCR/miR-4319/VAPB axis in development of this cancer [28]. Another mechanism of involvement of DANCR in the pathogenesis of breast cancer is mediated through enhancement of the EZH2 binding to the promoter of SOCS3, which results in suppression of expression of SOCS3. Up-regulation of SOCS3 or suppression of EZH2 has led to reversion of malignant features stimulated by DANCR [29].

Expression of DANCR has been found to be high in cisplatin-resistant gastric cancer cells. However, siRNA-mediated silencing of this lncRNA in SGC7901/DDP and BGC823/DDP cells has led to significant decrease in their survival and induction of apoptosis. Furthermore, DANCR up-regulation could up-regulate expression levels of MDR1 and MRP1 in cisplatin resistant gastric cancer cells [30]. Another study in gastric cancer cells has shown that KLF5 activates DANCR transcription. DANCR could act as a molecular sponge for miR-194 to suppress its expression and increase expression of AKT2, thus promoting gastric carcinogenesis through inhibition of autophagy [31]. Moreover, expression of DANCR in gastric cancer can be induced by SALL4 [32].

Table 1 summarizes the molecular axes mediating the effects of DANCR in the carcinogenesis, based on the results of in vitro studies.

**Animal studies**

Up-regulation of DANCR in osteosarcoma cells has been shown to promote xenograft tumor growth and lung metastases [2]. Critical roles of this lncRNA in induction of metastatic pathways have also been confirmed in animal models of colon cancer [22], nasopharyngeal carcinoma [73] and prostate cancer [85]. Moreover, results of experiments in animal models of cancer have suggested the impact of DANCR in resistance to sorafenib and cisplatin in hepatocellular carcinoma [18] and colon cancer [21], respectively. Moreover, bulk of evidence from investigations in xenograft models of cancer firmly supports the role of DANCR in induction of tumor growth (Table 2).

**Clinical studies**

Expression of DANCR has been constantly enhanced in osteosarcoma samples, and its up-regulation has been positively associated with size of tumors and their metastatic ability. In fact, it is regarded as an independent poor prognostic factor for osteosarcoma. Besides,
| Tumor type          | Interactions                          | Cell line                          | Function                                                                 | References |
|---------------------|---------------------------------------|------------------------------------|--------------------------------------------------------------------------|------------|
| Acute myeloid leukemia | miR-874-3p/ATG16L1 axis               | HL60, U937, and KG1a               | DANCR is involved in Ase-C resistance and promotes autophagy in HL60 cells via regulating ATG16L1 scattering | [33]       |
| Bladder cancer      | miR-335/VEGF-C axis                   | SW780, 5637, T24, UM-UC-3, SV-HUC-1, and T24 | Δ DANCR ↓ proliferation, migration, and invasion and lymphatic metastases | [7]        |
| IL-11-STAT3 signaling and COND1 | miR-149-5p/MI2 axis                  | 5637, SW780, UM-UC-3, T24 and SV-HUC-1 | Δ DANCR ↓ proliferation, migration, and invasion and EMT process         | [9]        |
| Breast cancer       | miR-335/VEGF-C axis                   | SW780, 5637, T24, UM-UC-3, SV-HUC-1, and T24 | Δ DANCR ↓ proliferation, migration, invasion and lymphatic metastases   | [7]        |
| miR-874-3p/ATG16L1 axis               | T24, 293T                             | UM-UC-3, T24 and 293T               | DANCR was found to promote bladder cancer progression                  | [8]        |
| miR-149-5p/MI2 axis                  | 5637, SW780, UM-UC-3, T24 and SV-HUC-1 | 5637, SW780, UM-UC-3, T24 and SV-HUC-1 | DANCR was found to promote bladder cancer progression                  | [8]        |
| miR-149-5p/MI2 axis                  | 5637, SW780, UM-UC-3, T24 and SV-HUC-1 | 5637, SW780, UM-UC-3, T24 and SV-HUC-1 | DANCR was found to promote bladder cancer progression                  | [8]        |
| miR-874-3p/ATG16L1 axis               | T24, 293T                             | T24, 293T                          | DANCR was found to promote bladder cancer progression                  | [8]        |
| Breast cancer       | miR-335/VEGF-C axis                   | SW780, 5637, T24, UM-UC-3, SV-HUC-1, and T24 | Δ DANCR ↓ proliferation, migration, invasion and lymphatic metastases   | [7]        |
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| Breast cancer       | miR-335/VEGF-C axis                   | SW780, 5637, T24, UM-UC-3, SV-HUC-1, and T24 | Δ DANCR ↓ proliferation, migration, invasion and lymphatic metastases   | [7]        |
| IL-11-STAT3 signaling and COND1 | miR-149-5p/MI2 axis                  | 5637, SW780, UM-UC-3, T24 and SV-HUC-1 | Δ DANCR ↓ proliferation, migration, and invasion and EMT process         | [9]        |
| Tumor type                  | Interactions                                                                 | Cell line                        | Function                                                                 | References |
|----------------------------|------------------------------------------------------------------------------|----------------------------------|--------------------------------------------------------------------------|------------|
| Colorectal cancer          | miR-518a-3p/MDM2 axis, Smad2/3 and p53                                         | HT29, HCT116, SW116, Caco-2, and FHC | Δ DANCR ↓ proliferation, viability, metastasis                          | [22]       |
|                            | ∆                                 | SW620, SW480, HCT116, HT29, Caco-2, and HCoEpiC | Δ DANCR ↓ proliferation, colony formation, and ↑ apoptosis               | [45]       |
|                            | MALAT1 and QK                     | HCT116, RKO, SW620, HT-29, and LoVo | DANCR inhibits Doxorubicin-induced apoptosis via enhancing the mRNA stability of MALAT1 and interacting with QK | [23]       |
|                            | miR-185-5p/HMGA2 axis             | NCM460 and the CRC cell lines LoVo, SW620, SW480, and HT29 | Δ DANCR: ↓ proliferation, migration, invasion and cell cycle progression, and ↑ apoptosis | [46]       |
|                            | KAT6A                            | LOVO, SW480, HCT116, SW620, and HT29 | Δ DANCR: ↓ proliferation, cell cycle progression, and tumorigenesis | [47]       |
|                            | miR-145-5p/NRAS axis              | –                                | DANCR showed an indirect effect on NRAS expression levels via targeting miR-145-5p | [48]       |
|                            | miR-577/HSP27 axis                | HT29, HCT116, SW480, and LOVO and NCM460 | Δ DANCR: ↓ proliferation and metastasis                                  | [49]       |
|                            | miR-214                           | KLE, RL95-2, Ishikawa, AN3CA, and HEC-18 | Δ DANCR: ↓ proliferation and ↑ apoptosis                                   | [50]       |
| Endometrial carcinoma      | ZNF750, and miR-4707-3p/FOXC2 axis                                           | SHEE, KYSE140, KYSE150, KYSE180, KYSE410, KYSE5, KYSE450, Colo660N, and ECA109 | Down-regulation of ZNF750 induces DANCR expression, thus inhibits miR-4707-3p to interact with FOXC2, resulting in enhanced FOXC2 signaling and angiogenesis | [51]       |
| Esophageal squamous cell carcinoma | miR-33a-5p/ZEB1 axis               | EC9706, EC109, EC1, KYSE130, and Het-1A | ↑↑ miR-33a-5p (a target of DANCR): ↓ proliferation and metastasis       | [52]       |
|                            | –                                | ECA109 and TE-1                  | Δ DANCR: ↓ proliferation, migration, invasion, and ↑ apoptosis           | [53]       |
| Gastric cancer             | MDR1 and NRP1                     | SGC7901 and BGC823              | Δ DANCR: ↓ survival and increased apoptosis                              | [30]       |
|                            | miR-19a/AKT2 axis and              | SGC7901, MGC-803, NO-Ni87, and GES-1 | Δ DANCR: ↓ viability, ↑ autophagy, and apoptosis                          | [31]       |
|                            | SALL4 and β-catenin pathway       | GES-1, BGC-823, MGC-803, MGC-27 and MKN-45 | Δ DANCR: ↓ proliferation, migration, invasion and EMT process, ↑ cell cycle arrest and apoptosis                                          | [32]       |
|                            | –                                | SGC7901, MGC803, and MKN-45      | Δ DANCR: ↓ proliferation, and ↑ cell cycle arrest                       | [54]       |
Table 1 (continued)

| Tumor type               | Interactions                                                                 | Cell line                      | Function                                                                                     | References |
|--------------------------|------------------------------------------------------------------------------|--------------------------------|-----------------------------------------------------------------------------------------------|------------|
| Glioma                   | miR-135a-5p/BMI1 axis                                                       | LN229, U251 and NHAs          | Δ DANCR ↓ proliferation, migration and invasion                                               | [55]       |
|                          | miR-33a-5p                                                                  | HEB, U87, U251, LN22 9 and T98G | Δ DANCR ↓ proliferation, migration, and EMT process, and ↑ apoptosis                        | [56]       |
| Wnt/β-catenin signaling  | miR-33a-5p, miR-33b-5p, miR-1-3p, miR-206, and miR-613/AXL axis and PI3K/Akt/NF-κB signaling pathway | U87MG, U251MG, LN18 and U138MG | ↑↑ DANCR ↓ sensitivity of glioma cells to cisplatin, DANCR up-regulates AXL to activate PI3K/Akt/NF-κB signaling pathway | [57]       |
|                          | miR-634/RAB1A axis                                                          | U251, U118, LN229, U87MG, and NHAs | Δ DANCR ↓ proliferation and ↑ G0/G1 phase arrest                                            | [58]       |
|                          | miR-216a/LGR5, PI3K/AKT                                                    | SHG-44, U87MG, U118MG, and U251MG | Δ DANCR ↓ proliferation, migration, invasion, angiogenesis, and ↑ phase arrest and apoptosis | [59]       |
|                          | IGF2B2, FOXO1, PID1                                                         | U251MG, LN229, LN18, T98G, and HEK293T | IGF2B2 increases DANCR stability and decreases DANCR methylation. DANCR indices ubiquitination of FOXO1 via interacting with FOXO1. PID1 promoted by FOXO1 enhances the chemotherapy sensitivity of GBM cells | [60]       |
|                          | miR-125b-5p/MAPK pathway axis                                              | HepG2 and Huh-7 cells         | Δ DANCR ↓ migration, invasion                                                                | [61]       |
| Hepatocellular carcinoma | miR-216a-5p/KLF12 axis                                                      | Huh7, HepG2 and LO2 cells     | Δ DANCR ↓ proliferation, migration, invasion and ↑ apoptosis                                | [62]       |
|                          | miR-222-3p/ATG7 axis                                                        | Bel-7402, HepG2, Huh7, MHCC97H and LO2 | Δ DANCR ↓ proliferation and autophagy                                                        | [63]       |
|                          | PSMD10-IL-6/STAT3 signaling axis                                           | HEK-293T, Huh7 and HepG2     | DANCR promotes sorafenib resistance via PSMD10-IL-6/STAT3 signaling axis                     | [64]       |
|                          | CTNNB1                                                                       | HCC cells                     | DANCR is involved in stemness features of hepatocellular carcinoma by derepression of CTNNB1 | [65]       |
|                          | miR-27a-3p/ROCK1/LMK1/COFLIN1 pathway axis                                 | MHCC-97L, Huh7, HCC-LM3, HepG2, MHCC-97L, Hep38, SMMC-7721 and LO2 | Δ DANCR ↓ proliferation, and metastasis                                                      | [66]       |
|                          | β-catenin pathway                                                           | SMMC-7721 and HCCLM3          | Δ DANCR ↓ proliferation and metastasis                                                        | [67]       |
|                          | miR-216a                                                                     | BEAS-2B, NCI-H1299, A549, and NCI-H1975 | Δ DANCR ↓ proliferation and colony formation                                                  | [68]       |
| Tumor type            | Interactions                                      | Cell line                          | Function                                      | References |
|-----------------------|---------------------------------------------------|------------------------------------|-----------------------------------------------|------------|
| Lung cancer           | miR-1225-3p/Erbb2 axis                            | 16HBE, A549, SPCA1, H1299 and H1975 | ∆ DANCR ↓ Migration and Invasion              | [11]       |
|                       | miR-214-5p/CI21 axis                              | 16HBE, A549, SPCA1, H1299 and H358 | ∆ DANCR ↓ proliferation and ↑ apoptosis       | [13]       |
|                       | miR-496/mTOR axis                                 | A549, H1299, H358, (HEK) 293T cells and HBE | ∆ DANCR ↓ proliferation, migration and invasion and ↑ apoptosis | [12]       |
|                       | HMGA2                                             | 16HBE, SPCA1, A549, H1299 and H1975 | ∆ DANCR ↓ invasion ▲ DANCR ↑ invasion via increasing HMGA2 | [63]       |
|                       | miR-216a and Wnt/β-catenin pathway                | A549, H1975, H1755, H1944, H2087, H358, H661 and H1299 | ∆ DANCR ↓ proliferation, stemness, migration, invasion | [14]       |
|                       | p21                                               | A549, H1299, H358 and BEAS-2B      | ∆ DANCR ↓ proliferation, migration, inva‑sion EMT process, ▲ apoptosis and cell cycle arrest | [64]       |
|                       | miR-138/Sox4 axis                                 | NHBE, HEK-293T, AS49, H1299, H460, SK-MES-1, and Calu-3 | ∆ DANCR ↓ proliferation, migration, invasion EMT process, and ↑ apoptosis | [65]       |
|                       | miR-758-3p                                        | SPC-A, NCL-H1650, NCL-H1975, SK-MES-1, A549, NCL-H358, NCL-H1299 and 16HBE | ∆ DANCR ↓ viability, proliferation and ↑ cell cycle arrest | [66]       |
|                       | –                                                 | HT-29 and F-HE                      | △ DANCR ↓ proliferation, migration, invasion EMT process, and metastasis | [67]       |
| Multiple myeloma      | miR-135b-5p/KLF9 axis                             | MM cells                           | △ DANCR ↓ proliferation, migration, and invasion | [68]       |
|                       | IL-6/JAK1/STAT3 signaling                        | NPM460, CNE1, CNE2, HNE1, HNE2, HONE1, 5–8 F, and 6-10B | △ DANCR ↓ proliferation and invasion IL-6 is involved in DANCR expression upregulation via an STAT3-dependent manner DANCR interacts with STAT3 and enhances JAK1 binding to STAT3 | [69]       |
| Nasopharyngeal carcinoma | RBM3 and SOX2                                    | C666-1, CUNE-1, HNE-1, CNE1, CNE2, and NP69 | △ DANCR ↓ proliferation, colony formation DANCR functions as an oncogene via binding to RBM3 to stabilize SOX2 mRNA | [70]       |
|                       | PTEN, AKT                                         | 5-8F, SUNE-1, C666-1, and NP469    | △ DANCR ↓ proliferation, colony formation, and ↑ apoptosis DANCR is involved in expression of PTEN | [71]       |
|                       | EZH2 and PTEN                                     | SUNE-1 and 5-8F                    | △ DANCR ↓ cell growth and migration DANCR mediates the binding of EZH2 on PTEN promoter to down-regulate PTEN expression | [72]       |
|                       | HIF-1α, NF90/NF45 complex                         | SUNE-1, HONE-1, CNE-1, CNE-2, HNE-1, 5-8F, 6-10B and C666-1, and S18 and S26 | △ DANCR ↓ migration and invasion DANCR increases stability of HIF-1α mRNAs | [73]       |
|                       | miR-338-3p/B4GALT3 axis                           | neuroblastoma cells                | △ DANCR ↓ proliferation and ↑ apoptosis | [74]       |
| Neuroblastoma         | miR-216a-5p/Blk-2/KLF12 axis                      | SCC9, SCC15, SCC23, CAL-27 and Tca8113, and NHO-Ks | △ DANCR ↓ proliferation, migration, invasion, and ↑ apoptosis | [75]       |
| Oral squamous cell carcinoma | miR-335-5p/miR-1972/ROCK1 axis                   | MG-63, U2OS, MNNG/HOS, 1,438 and hFOB 1.19 | △ DANCR ↓ proliferation, migration, invasion and metastasis | [3]        |
| Tumor type                        | Interactions                      | Cell line          | Function                                                                 | References |
|----------------------------------|-----------------------------------|--------------------|-------------------------------------------------------------------------|------------|
| Osteosarcoma                     | miR-33a-5p/AXL axis, P3K-Akt signaling pathway | MG63, U2OS, SaOS2, HOS, and 143B | ➲ DANCR ↓ proliferation, migration, invasion | [2]        |
|                                  | miR-148/MSI2 axis                 | HFOB1.19 and Saos-2 | ➲ DANCR ↓ proliferation, migration, invasion | [4]        |
|                                  | miR-216a-5p/SOS5 axis             | MG63, U2OS, 143B and hFOB 1.19 | ➲ DANCR ↓ proliferation, migration, invasion and autophagy and ↑ apoptosis | [5]        |
|                                  | METTL3                             | Saos-2, SJSA-1, MG63, HOS, and U-2 OS, and hFOB 1.19 | ➲ DANCR ↓ proliferation, migration, invasion | [6]        |
|                                  | SP1                                | CAOV3, SKOV3, A2780 | ➲ DANCR ↓ viability, migration and invasion | [76]       |
|                                  |                                    |                    | SP1 could induce DANCR expression by binding to the promoter region of DANCR in ovarian cancer tissues and cells |            |
|                                  |                                    |                    | ➲ DANCR ↓ viability, migration, and invasion, and ↑ apoptosis | [77]       |
|                                  |                                    |                    | ➲ DANCR ↓ tube formation, angiogenesis, and invasion | [78]       |
|                                  |                                    |                    | ↑↑ DANCR: ↑ proliferation, migration via negatively regulating UPF1 level | [79]       |
|                                  |                                    |                    | ➲ DANCR ↓ proliferation, migration, and invasion and EMT process | [24]       |
|                                  |                                    |                    | ➲ DANCR ↓ growth and metastasis | [25]       |
|                                  |                                    |                    | ➲ DANCR ↓ proliferation, and colony formation | [80]       |
|                                  |                                    |                    | ➲ DANCR ↓ proliferation and invasion | [26]       |
|                                  |                                    |                    | ➲ DANCR ↑ Paclitaxel Sensitivity | [81]       |
|                                  |                                    |                    | ➲ DANCR ↑ proliferation, migration, and ↓ EMT process | [25]       |
|                                  |                                    |                    | ➲ DANCR ↑ proliferation and migration, and ↓ apoptosis | [83]       |
|                                  |                                    |                    | ➲ DANCR ↑ sensitivity to docetaxel | [84]       |
|                                  |                                    |                    | ➲ DANCR ↑ migration and invasion | [85]       |
|                                  |                                    |                    | ➲ DANCR ↑ invasion and metastasis | [86]       |
|                                  |                                    |                    | ➲ DANCR ↓ proliferation, migration and invasion, and ↑ apoptosis | [87]       |
|                                  |                                    |                    | ➲ DANCR ↓ proliferation, invasion, and EMT process | [88]       |
|                                  |                                    |                    | ➲ DANCR ↓ proliferation, viability, migration and invasion | [89]       |
|                                                          |                                    |                    |                                                          |            |
| Ovarian cancer                   | miR-214/TGF-β axis                | A2780 and SKOV3     | ➲ DANCR ↓ viability, migration and invasion, and ↑ apoptosis | [76]       |
|                                  | miR-145/VEGF axis                 | A2780, PA-1, SKOV3, HO8910, and HOEC | ➲ DANCR ↓ tube formation, angiogenesis, and invasion | [78]       |
|                                  | URF1                               | IOSE-386, SKOV-3, OVCAR3, HO8910, and HEY | ↑↑ DANCR: ↑ proliferation, migration via negatively regulating URF1 level | [79]       |
|                                  | miR-33b/MMP16 axis                | AsPC-1, PANC-1, CFPA-1, SW1990, BxPC-3 and HPDE6-C7 | ➲ DANCR ↓ proliferation, migration, and invasion and EMT process | [24]       |
|                                  |                                    |                    | ➲ DANCR ↓ proliferation, and colony formation | [80]       |
|                                  |                                    |                    | ➲ DANCR ↓ proliferation and invasion | [26]       |
|                                  |                                    |                    | ➲ DANCR ↑ Paclitaxel Sensitivity | [81]       |
|                                  |                                    |                    | ➲ DANCR ↑ proliferation, migration, and ↓ EMT process | [25]       |
|                                  |                                    |                    | ➲ DANCR ↑ proliferation and migration, and ↓ apoptosis | [83]       |
|                                  |                                    |                    | ➲ DANCR ↑ sensitivity to docetaxel | [84]       |
|                                  |                                    |                    | ➲ DANCR ↑ migration and invasion | [85]       |
|                                  |                                    |                    | ➲ DANCR ↑ invasion and metastasis | [86]       |
|                                  |                                    |                    | ➲ DANCR ↓ proliferation, migration and invasion, and ↑ apoptosis | [87]       |
|                                  |                                    |                    | ➲ DANCR ↓ proliferation, invasion, and EMT process | [88]       |
|                                  |                                    |                    | ➲ DANCR ↓ proliferation, viability, migration and invasion | [89]       |
| Pancreatic cancer                | miR-214-5p/E2F2 axis              | PANC-1, SW1990, CAPAN-1, BxPC-3, AsPC-1 and HPDE6-C7 | ➲ DANCR ↓ proliferation, migration, and invasion and EMT process | [26]       |
|                                  | miR-33a-5p/AXL axis               | Panc1, Panc28, AsPC1, MiaPaCa2 and BxPC3 and HPDE3 | ➲ DANCR ↓ proliferation, and colony formation | [80]       |
|                                  | miR-135a /NLRP3 axis              | BxPC-3, MiaPaCa-2, CFPA-1, PANC-1, SW1990 and HPDE6-C7 | ➲ DANCR ↓ proliferation and invasion | [26]       |
|                                  | miR-135a                          | RWPE-1, PC3, C4-2, and DU145 | ➲ DANCR ↑ Paclitaxel Sensitivity | [81]       |
| Prostate cancer                  | miR-185-5p/LASP1 axis and FAK/P13K/AKT/GSK3β/ Snail pathway | C4-2, PC3, DU145, LNCaP, 22Rv1, and RVPE-1 | ➲ DANCR ↓ proliferation, migration, invasion, G1-S transition and EMT process | [82]       |
|                                  | miR-214-5p/TGF-β axis             | DU145, 22Rv1, RC-9.2a, PC-3M and RVPE-1 | ↑↑ DANCR: ↑ proliferation and migration, and ↓ apoptosis | [83]       |
|                                  | miR-34a-5p/JAG1 axis              | DU145 and PC3       | ➲ DANCR ↑ sensitivity to docetaxel | [84]       |
|                                  | TIP30/3, E2H2                     | CWR22RV1, PC-3, and C4-2B | ➲ DANCR ↓ migration and invasion | [85]       |
|                                  |                                    | 786-O and ACHN      | ↑↑ DANCR: ↑ proliferation, migration, and ↓ apoptosis | [86]       |
|                                  |                                    |                    | ➲ DANCR ↓ proliferation, invasion, and EMT process | [88]       |
|                                  |                                    |                    | ➲ DANCR ↓ proliferation, viability, migration and invasion | [89]       |
| Renal cell carcinoma             | miR-34c and miR-613/ MMP-9 axis   | Weri-Rb1, Y79, SO-Rb90, HXO-RB44, ARPE-19, and hTERT-RPE1 | ➲ DANCR ↓ proliferation, invasion, and EMT process | [87]       |
| Retinoblastoma                   | miR-135a-5p/KLF8 axis and MMP-2/9 | SCC9, TSCCA, TCO-8113, CAL-27 cells, and SCC9 | ➲ DANCR ↓ proliferation, viability, migration and invasion | [88]       |

Δ: knock-down or deletion, EMT: epithelial–mesenchymal transition, TNBC: Triple negative breast cancer, GBM: glioblastoma
| Tumor type          | Results                                                                 | References |
|---------------------|-------------------------------------------------------------------------|------------|
| Bladder cancer      | Δ DANCR: ↓ tumor volume, tumor growth and metastasis                      | [8]        |
|                     | Δ DANCR: ↓ tumor weight, and tumor growth                                 | [9]        |
| Breast cancer       | Δ DANCR: ↓ tumor growth                                                  | [27]       |
|                     | Δ DANCR: ↓ tumor growth                                                  | [29]       |
|                     | Δ DANCR: ↓ tumor growth                                                  | [35]       |
|                     | Δ DANCR: ↓ tumor weight, tumor volume                                    | [36]       |
|                     | Δ DANCR: ↓ tumor growth                                                  | [37]       |
|                     | RGD-PEG-ECO/siDANCR nanoparticles: ↓ proliferation                       | [38]       |
| Cervical cancer     | Δ DANCR: ↓ tumor growth                                                  | [40]       |
|                     | Δ DANCR: ↓ tumor weight and tumor growth                                  | [41]       |
|                     | ↑ miR-665 (a target of DANCR): ↓ tumor weight and tumor growth           | [42]       |
| Cholangiocarcinoma  | Δ DANCR: ↓ tumor growth                                                  | [43]       |
|                     | Δ DANCR: ↓ tumor weight and tumor growth                                  | [44]       |
| Colon cancer        | Δ DANCR: ↓ tumor growth                                                  | [21]       |
|                     | Δ DANCR: ↓ tumor formation and metastasis                                | [22]       |
|                     | Δ DANCR: ↓ tumor volume, and tumor growth                                | [45]       |
| Colorectal cancer   | ↑↑ DANCR: ↑ tumor volume and tumor growth                                | [49]       |
| Gastric cancer      | Δ DANCR: ↓ tumor growth                                                  | [31]       |
|                     | Δ DANCR: ↓ tumor weight, tumor volume, tumor size and proliferation      | [32]       |
|                     | ↑↑ DANCR: ↑ cell growth and tumorigenicity                              | [54]       |
| Glioma              | Δ DANCR: ↓ tumor weight, tumor volume, and tumor growth                  | [55]       |
|                     | Δ DANCR: ↑ apoptosis-inducing roles of cisplatin in vivo                 | [58]       |
| Hepatocellular carcinoma | Δ DANCR: ↓ sorafenib resistance                                       | [18]       |
|                     | Δ DANCR: ↓ cell vitality, tumor shrinkage                                | [19]       |
|                     | Δ DANCR: ↓ tumor growth                                                  | [20]       |
|                     | Δ DANCR: ↓ tumor growth                                                  | [62]       |
| Lung cancer         | Δ DANCR: ↓ tumor growth                                                  | [10]       |
|                     | Δ DANCR: ↓ tumor growth                                                  | [12]       |
|                     | Δ DANCR: ↓ tumor weight, tumor volume and tumor growth                   | [65]       |
|                     | Δ DANCR: ↓ tumor growth                                                  | [66]       |
|                     | Δ DANCR: ↓ tumor volume                                                  | [67]       |
| Nasopharyngeal carcinoma | Δ DANCR: ↓ tumor size and tumor growth                                   | [71]       |
|                     | Δ DANCR: ↓ tumor volume and tumor weight                                 | [72]       |
|                     | Δ DANCR: ↓ invasion and metastasis                                       | [73]       |
| Oral squamous cell carcinoma | Δ DANCR: ↓ tumor weight, tumor volume, and tumor growth                  | [75]       |
| Osteosarcoma        | ↑↑ DANCR: ↑ tumor growth and metastasis                                  | [3]        |
|                     | Δ DANCR: ↓ tumor size and tumor volumes                                 | [2]        |
|                     | Δ DANCR: ↓ tumor growth and autophagy                                    | [5]        |
|                     | Δ METTL3: ↓ tumor volumes (DANCR could be a target of METTL3)            | [6]        |
| Ovarian cancer      | Δ DANCR: ↓ tumor weight, tumor volume, and tumor growth                  | [78]       |
| Pancreatic cancer   | DANCR was up-regulated as pancreatic cancer progressed                   | [89]       |
|                     | Δ DANCR: ↓ tumor growth                                                  | [25]       |
| Prostate cancer     | Δ DANCR: ↓ tumor weight, tumor volume, and tumor growth                  | [84]       |
|                     | Δ DANCR: ↓ metastasis                                                    | [85]       |
| Tongue squamous cell carcinoma | Δ DANCR: ↓ tumor growth and tumor formation                             | [88]       |

Δ: knock-down or deletion, NOD-SCID-gamma: severe combined immunodecient, GBM: glioblastoma
Table 3  Dysregulation of DANCR in clinical samples

| Tumor type   | Samples                                      | Expression (tumor vs. normal) | Kaplan–Meier analysis (Impact of DANCR dysregulation) | Univariate/multivariate cox regression | Association of dysregulation of DANCR with clinical data | References |
|--------------|----------------------------------------------|------------------------------|-------------------------------------------------------|---------------------------------------|----------------------------------------------------------|------------|
| Bladder cancer | 120 PTN                                      | Up                           | Shorter OS and DFS                                    | High levels of DANCR were an independent prognostic factor for shorter OS | LN metastasis status, tumor stage, histological grade     | [8]        |
|              | 106 PTN                                      | Up                           | –                                                     | –                                     | Higher histological grade and advanced TNM stage          | [9]        |
| Breast cancer | TCGA dataset                                 | Up in TNBC                   | Shorter OS                                            | –                                     | Bigger tumor size                                         | [27]       |
|              | 60 triple-negative (TNBC) type, 15 HER2 type, 15 Luminal A type, and 15 Luminal B type, and 10 normal breast tissues |                       | –                                                     | –                                     | Advanced tumor grades or lymph node metastasis           | [28]       |
|              | 30 PTN                                       | Up                           | –                                                     | –                                     | –                                                        | [28]       |
|              | TCGA database                                | Up                        | –                                                     | –                                     | –                                                        | [29]       |
|              | 46 PTN                                       | Up                           | –                                                     | –                                     | –                                                        | [34]       |
|              | 57 PTN                                       | Up                           | Shorter OS                                            | –                                     | Lower differentiation degree of TNBC cells               | [35]       |
|              | 35 TNBC tissues, 52 adjacent normal breast tissues and 25 non-TNBC breast tissues | Up-regulation of TUFT1 (which induces DANCR expression) in TNBC tissues | Shorter OS | – | – | [36] |
|              | 120 BC patients, 70 8BBD patients, and 105 healthy controls | Up in BC patients | Shorter OS | DANCR was found to be an independent risk factor for BC | Lymph node metastasis, ER status, HER2 status, and TNM stage | [90]       |
|              | Five GEO datasets: 657 breast tumors 50 TNBC and 50 non-TNBC tissues | Up in TNBC tissues | – | – | – | [93] |
|              | 63 PTN                                       | Up                           | Shorter OS                                            | –                                     | –                                                        | [37]       |
| Breast cancer | TCGA database: 790 BCa tissues and 104 normal tissues 12 TNBC patients and 4 normal controls | Up                           | –                                                     | –                                     | –                                                        | [38]       |
|              | 2192 samples from 21 studies                 | Up                           | –                                                     | –                                     | –                                                        | [94]       |
| Tumor type               | Samples                          | Expression (tumor vs. normal) | Kaplan–Meier analysis (impact of DANCR dysregulation) | Univariate/multivariate cox regression | Association of dysregulation of DANCR with clinical data                                                                 | References |
|-------------------------|----------------------------------|------------------------------|------------------------------------------------------|---------------------------------------|-----------------------------------------------------------------------------------------------------------------------------|------------|
| Cervical cancer         | 65 PTN                           | Up                           | Shorter OS                                           | –                                    | Advanced stage, larger tumors, advanced FIGO stage and lymph node metastasis                                               | [39]       |
|                         | 82 PTN                           | Up                           | Shorter OS                                           | –                                    | Large tumor size, advanced FIGO stage                                                                                         | [40]       |
|                         | 112 PTN                          | Up                           | –                                                    | –                                    | Histological type, tumor staging, infiltrating muscle depth and lymphatic metastasis                                             | [41]       |
|                         | 33 PTN                           | Down-regulation of miR-665 (a target of DANCR) Up-regulation of DANCR | Shorter OS                                           | –                                    | Tumor size, distant metastasis, advanced TNM stage                                                                         | [42]       |
| Cholangiocarcinoma      | 40 PTN                           | Up                           | Shorter OS                                           | –                                    | Tumor size, TNM state and lymph node metastasis                                                                            | [43]       |
|                         | GEO database (GSE76297) 17 PTN    | Up                           | –                                                    | –                                    | –                                                                                                                          | [44]       |
| Colon cancer            | 35 PTN                           | Up                           | –                                                    | –                                    | –                                                                                                                          | [21]       |
|                         | 69 PTN                           | Up                           | Shorter OS                                           | –                                    | –                                                                                                                          | [22]       |
| Colorectal cancer       | 50 PTN                           | Up                           | –                                                    | –                                    | TNM stage and positive lymph node metastasis                                                                            | [46]       |
|                         | 80 colorectal cancer patients and 10 normal colon tissues | Up                           | Shorter OS                                           | –                                    | Clinical stages                                                                                                             | [47]       |
|                         | 40 PTN                           | Up                           | –                                                    | –                                    | –                                                                                                                          | [48]       |
|                         | GEO (GSE126092) and TCGA databases 15 PTN | Up                           | –                                                    | –                                    | TNM stages                                                                                                                 | [49]       |
|                         | 47 PTN                           | Up                           | –                                                    | –                                    | Clinical stage, nodal and metastasis classifications, and liver metastasis                                                  | [49]       |
| Colorectal cancer       | 104 PTN                          | Up                           | Shorter OS and DFS                                   | –                                    | TNM stage, histologic grade, and lymph node metastasis                                                                     | [96]       |
| Endometrial carcinoma   | 27 patients and 18 normal controls | Up                           | –                                                    | –                                    | –                                                                                                                          | [50]       |
**Table 3 (continued)**

| Tumor type                        | Samples                                                                 | Expression (tumor vs. normal) | Kaplan–Meier analysis (impact of DANCR dysregulation) | Univariate/multivariate cox regression | Association of dysregulation of DANCR with clinical data | References |
|-----------------------------------|-------------------------------------------------------------------------|-------------------------------|-------------------------------------------------------|----------------------------------------|--------------------------------------------------------|------------|
| Esophageal squamous cell carcinoma| 51 PTN, Data of KMPlot tool (55 patients) and data of Linke-dOmic tool (178 patients) | Down-regulation of miR-33a-5p (a target of DANCR) | Shorter OS                                            | –                                      | Advanced TNM stage and lymph node metastasis            | [52]       |
| Gastric cancer                    | 32 PTN                                                                  | Up                            | –                                                     | –                                      | –                                                      | [53]       |
|                                   | 14 DDP-sensitive GC tissues and 14 DDP-resistant GC tissues             | Up in DDP-resistant           | –                                                     | –                                      | –                                                      | [30]       |
|                                   | TCGA database                                                           | Up                            | Shorter OS                                            | –                                      | Tumor size, TNM stage, invasion depth, and lymph node metastasis | [31]       |
|                                   | 86 PTN, 65 PTN, 55 patients and 39 healthy controls                    | Up                            | –                                                     | –                                      | Tumor size, TNM stage, lymphatic metastasis and invasion depth | [32]       |
| Glioma                            | 118 PTN, TCGA dataset                                                  | Up                            | Shorter OS                                            | –                                      | ­                                                       | [54]       |
|                                   | 82 glioma tissues and 10 normal brain tissues                           | Up                            | Shorter OS                                            | –                                      | Clinical grading and tumor size                         | [55]       |
|                                   | 86 PTN, 47 glioma patients and 14 normal tissues                       | Up                            | Shorter OS                                            | –                                      | Tumor grading                                          | [56]       |
|                                   | TCGA database                                                           | Up-regulation of IGF2BP2 (which increases DANCR stability) | –                                                     | –                                      | –                                                      | [57]       |
|                                   | 40 tumor tissues and 40 normal tissues                                 |                               | –                                                     | –                                      | Advanced tumor grade                                   | [59]       |
|                                   |                                                                          |                               | –                                                     | –                                      | –                                                      | [61]       |
| Tumor type               | Samples | Expression (tumor vs. normal) | Kaplan–Meier analysis (impact of DANCR dysregulation) | Univariate/multivariate cox regression | Association of dysregulation of DANCR with clinical data | References |
|-------------------------|---------|-------------------------------|----------------------------------------------------|---------------------------------------|----------------------------------------------------------|------------|
| Hepatocellular carcinoma | 62 PTN  | Up                            | Shorter OS                                         | –                                     | –                                                        | [17]       |
|                         | TCGA and GEPIA database 66 PTN | Up                            | Shorter OS                                         | –                                     | –                                                        | [18]       |
|                         | 13 HCC patients, 10 hepatitis, 10 with cirrhosis, and 10 normal database | Up in HCC patients              | Shorter OS                                         | High levels of DANCR were an independent prognostic factor | –                                                        | [19]       |
|                         | STARBASE and GEPIA database | Up                            | Shorter OS                                         | –                                     | –                                                        | [20]       |
|                         | 52 PTN  | 52 HCC patients, 29 patients with chronic hepatitis, 22 cirrhosis and 43 healthy controls | Up in HCC patients                      | –                                     | Microvascular and liver capsule invasion of HCC           | [62]       |
|                         | 23 PTN  | Down                          | –                                                  | –                                     | –                                                        | [92]       |
| Lung cancer             | 32 lung cancer tissues and 11 normal lung tissues | Up                            | Shorter OS                                         | Grade                                 | –                                                        | [10]       |
|                         | GSE130779: 8 PTN 48 PTN    | Up                            | Shorter OS                                         | TNM stage and lymph node metastasis   | –                                                        | [11]       |
|                         | 100 patients | Up                            | –                                                  | –                                     | –                                                        | [13]       |
|                         | 34 PTN   | Up                            | –                                                  | –                                     | –                                                        | [12]       |
|                         | 45 PTN   | Up                            | Shorter OS                                         | Advanced TNM stage, lymph node metastasis and a larger tumor size | –                                                        | [63]       |
|                         | TCGA database: lung 706 adenocarcinoma and 626 lung squamous cell carcinoma samples | Up                            | –                                                  | –                                     | –                                                        | [14]       |
|                         | 40 PTN   | Up                            | –                                                  | –                                     | –                                                        | [64]       |
|                         | 64 PTN   | Up                            | Shorter OS                                         | Larger tumor size, advanced TNM stage and lymph node metastasis | –                                                        | [65]       |
|                         | 128 PTN  | Up                            | –                                                  | –                                     | –                                                        | [66]       |
|                         | 40 PTN   | Up                            | –                                                  | –                                     | –                                                        | [67]       |
| Tumor type                        | Samples                  | Expression (tumor vs. normal) | Kaplan–Meier analysis (Impact of DANCR dysregulation) | Univariate/multivariate cox regression | Association of dysregulation of DANCR with clinical data | References |
|----------------------------------|--------------------------|------------------------------|-------------------------------------------------------|---------------------------------------|----------------------------------------------------------|------------|
| Nasopharyngeal carcinoma         | 10 PTN 100 PTN           | Up                           | Shorter OS                                           | –                                     | –                                                        | [70]       |
|                                  | 14 tumor tissues and 9 normal tissues 212 tumor tissue | Up                           | Shorter OS and DFS and metastasis-free survival      | DANCR expression and N stage were found to be independent prognostic factors | Lymph node metastasis                                    | [73]       |
| Oral squamous cell carcinoma     | 86 PTN                   | Up                           | Shorter OS                                           | –                                     | Histological grade, clinical staging and lymph node metastasis | [75]       |
| Osteosarcoma                     | 95 PTN                   | Up                           | Shorter OS                                           | –                                     | Lymph node metastasis and distant metastasis             | [3]        |
| Osteosarcoma                     | 34 PTN                   | Up                           | –                                                     | –                                     | –                                                        | [2]        |
| Osteosarcoma                     | 109 PTN                  | Up                           | –                                                     | –                                     | –                                                        | [4]        |
| Osteosarcoma                     | 45 PTN                   | Up                           | –                                                     | –                                     | –                                                        | [5]        |
| Osteosarcoma                     | 40 PTN                   | Up-regulation of METTL3 (DANCR could be a target of METTL3) | –                                                     | –                                     | –                                                        | [6]        |
| Ovarian cancer                   | 20 PTN 20 PTN            | Up                           | –                                                     | –                                     | –                                                        | [78]       |
| Pancreatic cancer                | 30 PTN                   | Up                           | –                                                     | –                                     | TNM staging and metastasis                               | [79]       |
| Pancreatic cancer                | 50 PTN                   | Up                           | Shorter OS                                           | –                                     | Tumor size, TNM stage, and lymph nodal metastasis        | [24]       |
| Pancreatic cancer                | 206 PTN                  | Up                           | Shorter OS and PFS                                   | DANCR was found to be an independent poor prognostic factor for both OS and PFS | Vascular invasion, advanced T stage, lymph node metastasis and advanced TNM stage | [80]       |
| Pancreatic cancer                | 68 PTN                   | Up                           | –                                                     | –                                     | TNM stage, N stage, and recurrence rates                 | [26]       |
| Papillary thyroid cancer         | GEO database (GSE33630, GSE50901, and GSE66783) 76 PTN | Down                         | –                                                     | –                                     | DANCR was found to be an independent protective factor for TNM stage | [91]       |
| Papillary thyroid cancer         | 112 PTN                  | Up                           | –                                                     | –                                     | Age and micro carcinoma                                  | [97]       |
| Tumor type             | Samples                                                                 | Expression (tumor vs. normal) | Kaplan–Meier analysis (impact of DANCR dysregulation) | Univariate/multivariate cox regression | Association of dysregulation of DANCR with clinical data | References |
|------------------------|--------------------------------------------------------------------------|------------------------------|-------------------------------------------------------|----------------------------------------|--------------------------------------------------------|------------|
| Prostate cancer        | 36 PTN                                                                   | Up                           | –                                                     | –                                      | –                                                      | [81]       |
|                        | 40 PTN                                                                   | Up                           | Shorter OS                                           | –                                      | Grade and metastasis                                   | [82]       |
|                        | 53 patients and 47 healthy controls                                      | Up                           | Shorter OS                                           | –                                      | PSA, Gleason score, T stage, N stage and M stage       | [83]       |
|                        | 15 DTX-sensitive and 14 DTX-resistant PC tissues                        | Up in DTX-resistant          | –                                                     | –                                      | –                                                      | [84]       |
| Renal cell carcinoma   | GEO database (GSE2547)                                                  | Up                           | –                                                     | –                                      | –                                                      | [85]       |
|                        | 24 PTN                                                                   | Down                         | –                                                     | –                                      | –                                                      | [86]       |
| Retinoblastoma         | 57 patients and matched health controls                                 | Up                           | Shorter OS                                           | –                                      | –                                                      | [87]       |

OS: Overall survival, TNM: tumor node metastasis, TCGA: Cancer Genome Atlas, DFS: disease-free survival, HCC: hepatocellular carcinoma, PFS: progression-free survival, TNBC: Triple negative breast cancer, BC: breast cancer, BBD: benign breast disease, DTX: docetaxel, DDP: cisplatin, DFS: disease-free survival, PTN: pairs of tumor and normal samples
in patient samples, DANCR expression has been positively correlated with AXL levels and negatively correlated with expression levels of miR-33a-5p [2]. DANCR over-expression has also been detected in lung cancer, principally in high-grade samples and aggressive tumors [10]. Expression assays in hepatocellular cancer tissues have revealed over-expression of DANCR and ATG7, and down-regulation of miR-222-3p. Notably, DANCR levels have been positively correlated with poor clinical outcome in these patients [17]. Another study in hepatocellular carcinoma has shown up-regulation of DANCR in tumor and plasma samples in correlation with microvascular and hepatic capsule invasion. Most remarkably, plasma levels of DANCR have shown more appropriate discriminatory power for separation of patients with hepatocellular carcinoma from healthy controls and patients with chronic hepatitis B compared to α-fetoprotein [62]. In breast cancer samples, over-expression of DANCR has been associated with involvement of lymph nodes as well as hormone receptor and HER2 expressions [90]. Cumulatively, almost all studies in clinical samples have shown up-regulation of DANCR in malignant samples compared with their non-malignant counterparts. Exceptions to this rule are few studies in renal cell carcinoma [86], papillary thyroid cancer [91] and hepatocellular carcinoma [92]. Table 3 shows dysregulation of DANCR in clinical samples.

Discussion
DANCR is regarded as an oncogene in almost all types of cancers. All conducted studies have indicated up-regulation of DANCR in cancer tissues/cell lines except for a single study in renal cell carcinoma [86]. Moreover, two studies in papillary thyroid carcinoma [91] and hepatocellular carcinoma [92] reported down-regulation of this lncRNA, in spite of the bulk of evidence regarding up-regulation of DANCR in these two types of cancers. In support of the oncogenic role of DANCR, several studies have indicated association between up-regulation of DANCR and poor clinical outcomes. Moreover, over-expression of DANCR has been more frequently detected in patients having advanced clinical stages and distant metastases.

Over-expression of DANCR has also been associated with resistance to anti-cancer agents such as cytarabine, sorafenib, cisplatin and docetaxel. These findings indicate that DANCR-targeting therapies might affect response of cancer cells to a wide array of drugs, possibly conquering multidrug resistance.

DANCR has also been shown to possess appropriate diagnostic power to differentiate patients with liver cancer from healthy persons or those with non-malignant liver disorders [62]. Since this expression assay has been conducted in plasma samples, it potentiates DANCR as a non-invasive marker for cancer detection.

Tens of tumor suppressor miRNAs have been shown to be sponged by DANCR, leading to release of miRNA targets from their inhibitory effects. DANCR can also regulate activity of several important cancer-related pathways such as PI3K/AKT/NF-κB, Wnt/β-catenin, ERK/SMAD, MAPK, IL-6/JAK1/STAT3, Smad2/3, p53, FAK/PI3K/AKT/GSK3β/Snail pathways. Since several signaling pathways are influenced by DANCR, drugs targeting this lncRNA are expected to affect numerous aspects of carcinogenesis, thus being effective in treatment of a wide range of cancers with different biological behaviors.

In addition, DANCR has interactions with a number of proteins including CTNNB1, RXRA, EZH2 and PRC2. Most importantly, interaction of DANCR with proteins that influence epigenetic marks shows the importance of DANCR in the regulation of gene expression.

Conclusion
Although several expression assays have assessed expression levels of DANCR in biological samples obtained from different types of cancers, the underlying cause of dysregulation of DANCR in cancer has not been identified. In addition, the impacts of genomic variants on expression of this lncRNA and possible associations between single nucleotide polymorphisms within DANCR gene and susceptibility to cancer have not been appraised yet. Thus, future investigations should focus on these aspects. High throughput sequencing techniques could facilitate answering to these questions in near future.

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Author contributions
SGF wrote the manuscript and revised it. MT and AB supervised and designed the study. TK, MS and BMH collected the data and designed the figures and tables. All authors read and approved the final manuscript.

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Availability of data and materials
The analyzed data sets generated during the study are available from the corresponding author on reasonable request.

Declarations
Ethics approval and consent to participate
All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent forms were obtained from all study participants. The study protocol was approved by the ethical committee of Shahid Beheshti University of Medical Sciences. All
methods were performed in accordance with the relevant guidelines and regulations.

Consent of publication
Not applicable.

Competing interests
The authors declare they have no conflict of interest.

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