Long non-coding RNA colon cancer-associated transcript 2: role and function in human cancers

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Abstract

Long non-coding RNAs (lncRNAs) are a family of non-protein-coding RNAs that span a length of over 200 nucleotides. Research reports have illustrated that lncRNAs are involved in various cellular processes and that their abnormal expression leads to the occurrence and development of various tumors. Colon cancer-associated transcript 2 (CCAT2) was first reported as an oncogene in colon cancer. LncRNA CCAT2 is abnormally expressed in hepatocellular carcinoma, cholangiocarcinoma, lung cancer, breast cancer, ovarian cancer, glioma, and other tumors. In tumor tissues, abnormally overexpressed CCAT2 can affect cell proliferation, migration, epithelial-mesenchymal transition, apoptosis, and other biological behaviors through endogenous RNAs mechanisms, various signaling pathways, transcriptional regulation, and other complex mechanisms. Additionally, the overexpression of CCAT2 is also closely related to the tumor size, tumor node metastasis (TNM) stage, survival time, and other prognostic factors, suggesting that it is a potential prognostic indicator. This article reviews the biological functions of CCAT2 and its mechanisms of action in tumors from previous studies. In this review, we attempt to provide a molecular basis for future clinical applications of lncRNA CCAT2.

Keywords: Cancer; CCAT2; Long non-coding RNA; Colon cancer-associated transcript 2

Introduction

The vast majority of the human genome is transcribed into non-coding RNAs (ncRNAs), with only a few genes encoding for proteins. ncRNAs can be divided into long non-coding RNAs (lncRNAs) and short non-coding RNAs according to their length. LncRNAs are a class of ncRNAs with a length of more than 200 nucleotides that include antisense RNAs, pseudogenes, long intergenic ncRNAs, and circular RNAs. A wide variety of pathophysiological mechanisms are mediated by these RNA molecules. LncRNAs play a role in the modulating of the expression of genes at both the transcriptional and post-transcriptional levels, as well as participating in a variety of molecular regulatory mechanisms. Studies have shown that the abnormal expression of lncRNAs is strongly associated with the proliferation, migration, invasion, metastasis, cell cycle arrest, and other processes of various cancer cell types.[1-3] In addition, lncRNAs have great potential as diagnostic or prognostic biomarkers and can be therapeutic targets in a variety of human cancers.[4-6]

Colon cancer-associated transcript 2 (CCAT2) is a 1752 bp lncRNA that was initially established to be an oncogene in colorectal cancer (CRC). CCAT2 is situated on chromosome 8q24.21, with its genomic locus containing the single nucleotide polymorphism (SNP) rs6983267,[7] which is related to an increased risk of tumorigenesis.[8-11] In recent years, many studies have focused on the relationship between CCAT2 and tumorigenesis, indicating that CCAT2 is highly expressed in gastric cancer (GC),[12-14] breast cancer,[15-17] cervical cancer,[9] glioma,[18-20] lung cancer,[21-23] and other cancers. Some studies have further shown that highly expressed CCAT2 might serve as a prognostic indicator for patients with cancer because it is related to the TNM stage,[24,25] lymph node metastasis (LNM),[1,26] higher cell viability and migration ability,[27,28] stronger chemotherapy resistance,[21,29] and shorter overall survival (OS).[30-33] CCAT2 is involved in the regulation of multiple molecular signaling pathways, including phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt),[28] Wnt/β-catenin,[22] and GSK3β/β-catenin signaling pathways.[34] Moreover, CCAT2 regulates the proliferation, apoptosis, migration, invasion, cell cycle, angiogenesis, and epithelial-mesenchymal transition (EMT) of tumor cells.

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000002286

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Chinese Medical Journal 2022;135(23)

Received: 18-02-2022; **Online:** 08-09-2022 **Edited by:** Yanjie Yin and Xiuyuan Hao

This review highlights the aberrant expressions of CCAT2 in various cancers and analyzes its clinical importance and relevance in cell proliferation, invasion, metastasis, EMT, and other important cancer processes. In addition, the role of CCAT2 as an important regulatory RNA in human cancers, its diagnostic and therapeutic potential in malignant tumors have also been discussed.

Pan-cancer Analysis of CCAT2

In 2020, Huang *et al*[35] conducted a pan-cancer analysis based on The Cancer Genome Atlas database and softwares such as StataSE 12.0, GEPIA2, and lncRNA Target (version: 2.0), demonstrating that CCAT2 is expressed at high levels in an aberrant manner in many tumor tissues as opposed to the corresponding normal tissues. Furthermore, the results also demonstrated that the elevated CCAT2 expression was associated with an unfavorable prognosis, TNM stage, clinical stage, and tumor size in patients with cancer. Gene Ontology enrichment analysis of CCAT2-related genes has shown the regulatory role of CCAT2-related genes in transcription, transcriptional regulation, mRNA stability, and other processes. Moreover, Kyoto Encyclopedia of Genes and Genomes enrichment analysis has shown that CCAT2 plays a key role in cancer-related signaling pathways, such as the Hippo signaling pathway, RNA degradation pathway, and cell cycle pathway. Therefore, preliminary bioinformatics analysis has revealed that CCAT2 performs an instrumental function in cancer, thus paving the way for future research.

Meta-analysis of CCAT2

Meta-analysis of CCAT2 has revealed the correlation between CCAT2 and clinical indices, such as progression-free survival (PFS), OS, LNM, distant metastasis (DM), clinical prognosis, and other indicators. Moreover, Fan *et al*[36] pointed out that elevated expression of CCAT2 was substantially correlated with an unfavorable OS and PFS. Additionally, the elevated CCAT2 expression was also considerably correlated with LNM, DM, and tumor stage. Furthermore, results of several other meta-analyzes on CCAT2[37-40] have revealed similar results. Therefore, high CCAT2 expression is a predictor of unfavorable DM, LNM, PFS, OS, and later tumor stages [Supplementary Figures 1–8, http://links.lww.com/CM9/B423].

CCAT2 in Human Cancers

Since CCAT2 was first discovered in colon cancer, increasing evidence has revealed its differential expression in other cancers, as well as its biological functions, clinical relevance, and related signaling pathways.

CRC

In 2013, Ling *et al*[7] first reported that CCAT2, which was shown to exhibit a high and aberrant expression in microsatellite-stable CRC, enhanced the proliferation, metastasis, as well as chromosomal instability of tumors. In 2017, Zhang *et al*[32] found that the upregulation of CCAT2 was related to poor cell differentiation, tumor infiltration, LNM, DM, and vascular infiltration. In addition, Yu *et al*[41] found that CCAT2, which was enriched in the nucleus, blocked the maturation of miR-145 and increased the expression of a variety of cancer stem cell (CSC) markers in colon cancer cells. In 2018, Barbagallo *et al*[42] demonstrated that CCAT2 was upmodulated in serum exosomes of CRC patients according to the findings from a qRT-PCR analysis. In 2019, Wang *et al*[43] found that CCAT2 exhibited a substantial overexpression in the exosomes and serum of patients suffering from CRC; however, no significant differences were identified in the level of CCAT2 in serum and exosomes. In 2020, Gao *et al*[44] verified that CCAT2 could promote growth and proliferation in addition to suppressing cell apoptosis of CRC cells via *in vitro* experiments. Chen *et al*[6] found that CCAT2 can induce chromosomal instability by blocking the BOP1 ribosomal biogenesis factor (BOP1)-aurora kinase B signaling pathway. More interestingly, Gharib *et al*[5] pointed out that CCAT2 in the stool of patients experiencing CRC might be used as a biomarker for the early detection of CRC. In 2021, Thean *et al*[4] discovered that the expression levels of c-Myc and CCAT2 in the tumors of metastasis-positive patients were significantly upregulated compared with that in metastasis-negative patients. In summary, CCAT2 is upregulated in microsatellite-stable CRC tissues, and it is significantly related to the proliferation, migration, invasion, LNM, prognosis, and other clinically relevant indicators of CRC cells. In addition, CCAT2 can disrupt the stability of chromosomes through its effect on molecules such as BOP1.

GC

In 2015, Gao *et al*[44] discovered that the expression level of CCAT2 was remarkably elevated in GC tissues in contrast with that in the normal tissues. In 2016, Wang *et al*[24] revealed that knocking out CCAT2 inhibited the migratory and invasive activities of GC cells. Further research reports have demonstrated that CCAT2 promotes the EMT of GC cells through the downmodulation of the E-cadherin expression and the upmodulation of the N-cadherin expression. In addition, results of RNA immunoprecipitation and chromatin immunoprecipitation have shown that CCAT2 interacts with the enhancer of zest homolog 2 (EZH2) to regulate the expression of E-cadherin and large tumor suppressor kinase 2, thus enhancing the proliferation and metastasis capacity of GC cells. In 2017, Wu *et al*[14] revealed a positive correlation between CCAT2 and nerve infiltration in patients with GC. In addition, Yu *et al*[13] discovered that inhibiting the CCAT2 expression might suppress the proliferation of GC cells and induce apoptosis and autophagy through the PI3K mechanistic target of rapamycin (mTOR) signaling pathway. In 2020, Lin *et al*[12] also found similar results.[13] In summary, CCAT2 is upregulated in GC tissues. In addition to being closely related to patient survival, prognosis, LNM, and nerve infiltration, CCAT2 can also regulate processes such as apoptosis, autophagy, and EMT.

Esophageal cancer

In 2015, Wang *et al*[45] demonstrated that CCAT2 was considerably overexpressed in esophageal squamous cell

carcinoma (ESCC) tissues and cells. Zhang *et al*[26] revealed a positive correlation between the CCAT2 levels and the proportion of positive lymph nodes, LNM, TNM stage, and poor OS. In 2019, Wang *et al*[46] found that small interfering RNAs targeting CCAT2 may effectively suppress the proliferative, migratory, and invasive capabilities of EC cells and mediate cell apoptosis by means of downregulating β-catenin expression, thereby inhibiting the EMT process. Furthermore, Wang *et al*[47] illustrated that CCAT2 negatively regulates the miR-145/p70S6K1 and p53 signaling pathways and that it promotes the resistance of EC cells to radiotherapy. Therefore, the overexpression of CCAT2 is common in EC cells and tissues. In addition to being related to the biological behavior of the tumor, CCAT2 also affects the efficacy of radiotherapy in EC.

Hepatocellular carcinoma (HCC)

In 2016, Zhou *et al*[48] illustrated that the expression levels of CCAT2 are upmodulated in HCC cell lines and tissues. In 2017, Xu *et al*[49] discovered a positive correlation between the levels of CCAT2 and LNM and vascular infiltration in patients with HCC. Further studies have found that CCAT2 can promote HCC progression by regulating snail family transcriptional repressor 2-induced EMT. In the same year, Chen *et al*[50] showed the presence of a positive feedback loop between CCAT2 and forkhead box M1. They pointed out that ultrasound-targeted microbubble destruction (UTMD)-mediated siRNA targeting of CCAT2 significantly inhibited tumor growth in mice. In 2019, Liu *et al*[51] used double-luciferase reporter gene detection to show that CCAT2 enhances the expression of N-myc downstream regulated 1 by enhancing its promoter activity, thus inducing cancer cell proliferation and metastasis. In addition, Fu *et al*[52] indicated that CCAT2 expression was significantly related to vascular infiltration, histopathological grade, DM, and TNM stage. In 2020, Niu *et al*[27] pointed out that CCAT2 induces the expression of MDM2 proto-oncogene by inhibiting the maturation of miR-145, thereby promoting the progression of HCC. In conclusion, overexpression of CCAT2 is observed in HCC cells and tissues and is related to tumor proliferation, metastasis, and the prognosis status of patients with HCC. The relationship between the CCAT2 expression and tumor proliferation was validated by UTMD *in vivo*.

Cholangiocarcinoma (CCA)

In 2018, Xu *et al*[53] discovered the aberrant overexpression of CCAT2 in CCA cells and tissues and that such overexpression was related to the TNM stage, lymph node infiltration, tumor size, and post-surgical recurrence. They showed that knocking out CCAT2 could result in the suppression of the proliferative, migratory, and invasive capabilities of CCA cells by means of the regulation of EMT and the promotion of cell apoptosis. In the same year, Bai *et al*[54] pointed out that the elevated level of CCAT2 expression was associated with the TNM stage, the extent of differentiation, and microvascular infiltration of intrahepatic cholangiocarcinoma. In a 2019 meta-analysis, Dai *et al*[55] pointed out that the elevated expression of CCAT family genes, especially *CCAT2*, was correlated with a shorter OS. This was the first meta-analysis to delve into the correlation between lncRNA expression and clinical indicators of patients with CCA. The study suggested that lncRNAs could be used as potential molecular biological markers for assessing the clinicopathology as well as the prognosis profiles of CCA patients. In summary, the aberrant overexpression of CCAT2 is observed in CCA cells and tissues, and CCAT2 is significantly related to the tumor size, metastasis, and TNM stage. Knocking out CCAT2 can inhibit cancer cell proliferation through the EMT process.

Osteosarcoma

In 2017, Yan *et al*[31] demonstrated an elevated expression level of CCAT2 in osteosarcoma cells and tissues, highlighting that the CCAT2 overexpression may enhance the proliferative ability, invasiveness, and EMT process of osteosarcoma cells. In 2018, Ruan *et al*[34] illustrated the positive correlation between the elevated expression level of CCAT2 and the tumor size, tumor stage, and unfavorable OS. In addition, knocking out CCAT2 can suppress the proliferative ability of osteosarcoma cells by means of the inhibition of the GSK3β/β-catenin signaling pathway. In 2019, Liu *et al*[56] found that the CCAT2/miR-200b/vascular endothelial growth factor axis performs an integral regulatory role in osteosarcoma via the PI3K/Akt and protein kinase AMP-activated catalytic subunit alpha 1 (AMPK) pathways. In 2021, Bi *et al*[57] performed a dual-Luciferase reporter gene assay and found that miR-143 can directly bind to CCAT2. After co-transfection with anti-miR-143 oligonucleotides, the function of CCAT2 in osteosarcoma cells was weakened. In summary, an abnormal overexpression of CCAT2 is observed in osteosarcoma cells and tissues and is related to tumor proliferation, migration, and stage. Knockout of CCAT2 can affect cell proliferation through signaling pathways, including AMPK and PI3K/Akt signaling pathways.

Lung cancer

In 2014, Qiu *et al*[58] pointed out the remarkable overexpression of CCAT2 in non-small cell lung cancer (NSCLC) tissues, with an average upregulation of 7.5 times. In 2016, Chen *et al*[59] demonstrated the association of the CCAT2 expression with the unfavorable prognosis of NSCLC patients. In the same year, Zhao *et al*[60] found that CCAT2 was overexpressed in NSCLC cells and that CCAT2 could promote tumorigenesis through Pokemon protein. In 2017, Li *et al*[23] used a lentivirus-mediated small hairpin RNA (shRNA) to knock out CCAT2 in NSCLC cell lines and found that CCAT2, as an oncogenic lncRNA, promotes proliferative and metastatic abilities of tumor cells via the Wnt/β-catenin pathway. In 2018, Zhao *et al*[22] used a siRNA to knock out CCAT2 in NSCLC cells, and reached conclusions similar to those of Li *et al*[23] In 2020, He *et al*[21] pointed out that the knockout of CCAT2 enhanced the susceptibility of cisplatin-resistant A549 cells to cisplatin and decreased the tumor volume in mice. In summary, CCAT2 is overexpressed in lung cancer cells and tissues and is correlated with tumor

proliferation, invasion, cisplatin resistance, and other phenotypes. Moreover, CCAT2 can promote the occurrence and development of tumors by upregulating the expression of Pokemon protein.

Gynecological tumors

Cervical cancer

In 2015, Cai *et al*[61] showed the upmodulation of CCAT2 expression in cervical squamous cell carcinoma (CSCC) tissues. Specifically, the elevated level of CCAT2 expression was significantly correlated with the Federation International of Gynecology and Obstetrics (FIGO) stage, LNM, and cervical invasion depth. In 2016, Wu *et al*[62] found that knocking out CCAT2 could inhibit the proliferative capability of cervical cancer cells, stimulate cell cycle arrest in the G1 phase, and trigger cell apoptosis. In 2018, Lazniak *et al*[9] found that compared with low-grade CSCC, CCAT2 rs6983267 SNP promoted Myc expression, and promoted the spread and rapid growth of tumors. In 2020, Wang *et al*[63] pointed out the elevated expression of CCAT2 in the serum of CSCC patients and that CCAT2 may be a non-invasive biological marker for the diagnosis of CSCC.

Ovarian cancer

In 2016, Huang *et al*[64] demonstrated the substantially elevated expression level of CCAT2 in ovarian cancer cells and tissues in contrast with the levels in normal tissues. In 2017, Hua *et al*[65] showed that knocking out CCAT2 could promote the apoptosis of ovarian cells and stimulate cell cycle arrest in the G0/G1 phase by targeting miR-424 as a competitive endogenous RNA (ceRNA). In the same year, Wang *et al*[66] showed that CCAT2 might at least partially promote the occurrence and progression of ovarian cancer via the Wnt/β-catenin signaling pathway. In 2018, Wang *et al*[67] pointed out that CCAT2 promotes the EMT process in cervical cancer cells through the Wnt/β-catenin signaling pathway, thereby influencing the specific mechanisms of ovarian cancer.

Breast cancer

In 2013, Redis *et al*[68] discovered the expression of CCAT2 in a majority of tissues from patients with breast cancer. In addition, CCAT2 has been shown to promote cell migration and chemical resistance of cancer cells to 5-fluorouracil. In 2015, Cai *et al*[69] confirmed that silencing of CCAT2 may suppress tumor formation and cell growth *in vivo* via the Wnt signaling pathway. In 2016, Caia *et al*[29] revealed an elevated level of CCAT2 expression in tamoxifen-resistant cells as opposed to that in tamoxifen-sensitive cells. In 2017, Wu *et al*[17] pointed out that downregulation of CCAT2 may suppress the proliferative, invasive, and migratory abilities of breast cancer cells and mediate cell apoptosis by regulating the TGF-β signaling pathway. Additionally, Deng *et al*[16] demonstrated a remarkable correlation between the high-level of CCAT2 expression and the LNM and TNM stage of patients with breast cancer. They also illustrated that CCAT2 inhibited the p15 expression in breast cancer cells by interacting with EZH2, thereby promoting the proliferative ability of breast cancer cells. In 2020, Xu *et al*[15] found that CCAT2 was specifically overexpressed in breast CSCs and triple-negative breast cancer (TNBC). Further research reports have shown that CCAT2 mediates the occurrence and progression of tumors in TNBC by upregulating the OCT4-polygalacturonase 1 expression and activating the Notch signaling pathway. In the same year, Redis *et al*[70] found that vitamin D could inhibit the development of breast cancer by targeting CCAT2.

Endometrial cancer

In 2017, Xie *et al*[28] illustrated the elevated expression of CAT2 in endometrial cancer tissues in contrast with the adjacent non-cancerous tissues. Knockout of CCAT2 may suppress the proliferative, migratory, and invasive abilities of cells contributing to apoptosis. In addition, CCAT2 targets miR-216b, and inhibition of miR-216b can reverse the effect of CCAT2 knockout on endometrial cancer cells. Further research found that miR-216b negatively regulates Bcl-2, and Bcl-2 can further activate the PTEN/PI3K/Akt and mTOR signaling pathways. Overall, the above results indicate that CCAT2 is capable of suppressing the proliferative and metastatic abilities of endometrial cancer cells by binding miR-216b to regulate PI3K/Akt and mTOR signaling pathways.

In summary, CCAT2 is abnormally overexpressed in cervical, ovarian, breast, endometrial, and other gynecological cancers. Moreover, CCAT2, which is correlated with tumor cell proliferation, migration, and cell cycle, can affect the biological behavior of tumors through the PI3K/Akt, Wnt/β-catenin signaling pathway. In addition, CCAT2 exerts certain functions in cancer drug resistance.

Glioma

In 2016, Guo *et al*[20] showed the upmodulation of CCAT2 expression in glioma tissues. In the same year, Zeng *et al*[71] found that CCAT2 is related to tumor size, tumor grade, and survival. In addition, CCAT2 can regulate the expression of EMT-related genes. In 2017, Lang *et al*[19] discovered that glioma cell exosomes might be absorbed by human umbilical vein endothelial cells (HUVECs) and that they increase the expression level of CCAT2 in HUVECs. CCAT2 can promote the migration and proliferation of HUVECs by activating vascular endothelial growth factor A (VEGFA) and TGFβ, inhibiting apoptosis, and inducing the formation of small arteries in the body. In 2020, Sun *et al*[18] found that CCAT2 shares complementary sequences with miR-424 and that miR-424 directly binds to the 3′-UTR of VEGFA. In addition, CCAT2 promotes the proliferative ability of glioma cells as well as endothelial angiogenesis by activating the PI3K/Akt signaling pathway. In summary, there is an overexpression of CCAT2 in glioma cells and tissues, and it is related to the tumor size, grade, proliferation, migration, and prognosis. Furthermore, CCAT2 can promote angiogenesis through exosomes.

Hematological cancers

Multiple myeloma (MM)

In 2020, Xu *et al*[72] demonstrated the upmodulation of the CCAT2 expression in the bone marrow and serum of patients with MM. The area under the curve (AUC) value of CCAT2 in serum was 0.899; the specificity was 83.00% and the sensitivity was 85.80%. In addition, CCAT2, IgA, hemoglobin (HGB), and beta-2-microglobulin (β2-MG) can substantially improve the sensitivity and AUC of MM diagnoses. Here, our current study shows that circulating CCAT2 in the serum might function as a promising tumor biomarker for MM.

Myeloid malignancies

In 2018, Shah *et al*[8] used allele-specific CCAT2 transgenic mice and confirmed that elevated CCAT2 expression can lead to myeloid malignancies. Further studies have shown the CCAT2 overexpression in the peripheral blood and bone marrow of patients with myelodysplastic/myeloproliferative neoplasms (MDS/MPN) and that increased CCAT2 expression leads to the global modulation of gene expression by means of EZH2 downregulation. In addition, Li *et al*[30] pointed out that the level of CCAT2 expression in patients with acute myeloid leukemia (AML) was remarkably elevated in contrast with the levels in healthy individuals and that the content of white blood cells in patients exhibiting elevated CCAT2 expression was higher in contrast with that in patients exhibiting low CCAT2 expression. Overexpression of CCAT2 can promote tumor cell proliferation and stimulate cell cycle arrest in the S phase. Inhibition of CCAT2 can induce cell cycle arrest in the G2/M phase.

In summary, CCAT2 is overexpressed in the blood and bone marrow of patients with hematological malignancies such as MM and AML and is related to tumor cell proliferation and poor prognosis.

Prostate cancer (PC)

In 2016, Zheng *et al*[73] demonstrated an elevated level of CCAT2 expression in PC cells and tissues in contrast with that in adjoining non-tumor tissues and normal cells. Knockout of CCAT2 stimulates the EMT process by reducing the N-cadherin expression and enhancing the level of E-cadherin expression. In 2020, He *et al*[74] found that knocking out CCAT2 might suppress the proliferative, migratory, invasiveness, and cell cycle of PC cells. The luciferase report experiment pointed out that CCAT2 could regulate the expression of transcription factor 7 like 2 (TCF7L2) and bind to miR-217. Further research has shown that the knockout of CCAT2 inhibited the Wnt/β-catenin signaling pathway in tumor cells by inhibiting the expression of TCF7L2. Overall, there is an overexpression of CCAT2 in PC cells and tissues, which is correlated with the proliferative, migratory, invasiveness, and other biological behaviors of tumor cells. Furthermore, it may affect the EMT process through the Wnt/β-catenin signaling pathway.

Thyroid cancer (TC)

In 2020, Xin *et al*[3] revealed elevated expression levels of CCAT2 in TC cell lines and tissues. Moreover, the level of CCAT2 in tissues was related to the T stage of the tumor and tumor metastasis. Downregulation of CCAT2 can inhibit the progression of TC by inhibiting the Wnt/β-catenin cascade, illustrating that inhibition of CCAT2 and Wnt/β-catenin signaling pathways may be a viable treatment strategy for TC. In addition, Fu *et al*[2] pointed out the strong correlation between the CCAT2 expression and the capsular infiltration, LNM, and tumor size of TC. After knocking out CCAT2, the proliferation ability and IC_{50} values of TC cells to Adriamycin and cisplatin were significantly decreased, while the opposite was observed after CCAT2 overexpression. Overall, an elevated level of CCAT2 expression is observed in TC cells and tissues and is related to tumor cell proliferation, migration, invasion, and capsular infiltration. Furthermore, CCAT2 is also involved in the resistance of TC to Adriamycin and cisplatin.

Renal cell carcinoma

In 2017, He *et al*[74] demonstrated a remarkable elevation in the level of CCAT2 expression in clear cell renal carcinoma cells and tissues, where it was positively associated with the tumor size and tumor stage. Inhibiting the expression of CCAT2 leads to decreased cancer cell proliferation, increased apoptosis, and activation of the Wnt/β-catenin signal pathway. Overexpression of CCAT2 yielded opposite results. He *et al*[74] used a mouse xenograft model and showed that knocking out the expression of CCAT2 can inhibit the growth of xenografts. In 2019, Wu *et al*[75] pointed out that knocking out CCAT2 could inhibit cell proliferation, colony formation, and invasion. Moreover, CCAT2 can promote the proliferative and invasive abilities of renal cell carcinoma cells by interacting with miR-320a. Overall, CCAT2 is found to be highly expressed in renal cell carcinoma cells and tissues and is closely related to tumor size, proliferation, and migration. Furthermore, *in vivo* experiments have shown that knocking out CCAT2 can inhibit tumor growth.

Oral squamous cell carcinoma (OSCC)

In 2016, Ouyang *et al*[76] reported a substantial elevation in the CCAT2 expression levels in OSCC tissues in contrast with adjoining tissues. Such elevated expression was related to the differentiation and pathological stage. *In vitro* studies have shown that inhibiting the expression of CCAT2 can suppress the proliferative abilities of cancer cells. In 2017, Ma *et al*[77] pointed out that the high expression of CCAT2 is associated with unfavorable tissue differentiation, T stage, and higher clinical stage, suggesting that CCAT2 is an effective prognostic biomarker for OSCC. Further experiments have shown that CCAT2 can inhibit the proliferation of OSCC cells through the Wnt/β-catenin pathway. Overall, CCAT2 is abnormally overexpressed in OSCC tissues and is related to the clinical and pathological stages of tumors. Knockout of CCAT2 can affect the malignant behavior of tumors through the Wnt/β-catenin pathway.

Other tumors

In pancreatic ductal cell carcinoma, Cai *et al*[78] found that, compared with normal pancreatic cells, CCAT2 expression was upregulated in tumor cells. Moreover, the survival probability of pancreatic cancer patients declines in the case where an increased expression of CCAT2 is present. CCAT2 silencing can inhibit the proliferative and invasive abilities of tumor cells, as well as inhibit the growth of xenograft tumors *in vivo*. Further research has demonstrated that CCAT2 performs a function in pancreatic ductal cell carcinoma through the MEK/ERK signaling pathway regulated by KRAS proto-oncogene. In pituitary tumors, Fu *et al*[79] discovered a remarkable upmodulation of CCAT2 in tumor tissues, and that the elevated expression level of CCAT2 is correlated with the unfavorable patient prognosis. Furthermore, E2F transcription factor 1 can activate the expression of CCAT2. Further studies have shown that CCAT2 interacts with pituitary tumor-transforming gene 1, a regulator of sister chromatid separation, to promote its stability. In addition, CCAT2, which is abnormally overexpressed in bladder cancer,[25] neuroblastoma,[1] and nasopharyngeal carcinoma,[80] is related to the biological behavior of the corresponding tumor cells. Corresponding functional tests have also confirmed the role of CCAT2 in tumorigenesis and development. The functions of CCAT2 in multiple human cancers are listed in Table 1.

CCAT2 SNPs and Cancer

SNPs can affect the expression and functions of genes and can perform an integral function in the occurrence and progression of tumors. The rs6983267 (G/T) SNP is distributed in the 8q24.21 region of the chromosome. Two types of alleles, namely G and T, exist. The G allele is correlated with a greater CRC risk than the T allele.[7] In addition, the rs6983267 SNP variant also increases the risk of PC, breast cancer, bladder cancer, and other tumors. Interestingly, this SNP, which is located in the c-Myc enhancer region,[3] can regulate the Wnt signaling pathway.[44] In 2013, CCAT2 was found for the first time in microsatellite-stable CRC, located at 8q24, containing rs6983267 SNP.[7] In 2016, Redis *et al*[82,83] pointed out that the two alleles G and T of CCAT2 SNP rs69832674 differ from one another in terms of glutamine metabolism. In the same year, Gong *et al*[11] found that CCAT2 rs6983267 is closely related to lung adenocarcinoma sensitivity and platinum-based chemotherapy responsiveness. In 2017, Shaker *et al*[33] demonstrated the association between CCAT2 rs6983267 GG and an increased risk of CRC. The serum levels of CCAT2 of such patients were higher than those of patients with the GT/TT genotype. Moreover, rs6983267 is a potential genetic marker of CRC susceptibility and is related to serum CCAT2 levels. In 2018, Lazniak *et al*[9] pointed out that the rs6983267 genotype is related to the CSCC stage and G2 and G3 differentiation. Compared with G/T carriers and T/T carriers, GG carriers have significantly higher Myc transcription levels. Compared with low-grade CSCC, rs6983267 SNP not only promotes the upregulation of the expression of Myc, but also promotes the rapid growth and metastasis of tumors. In the same year, Shah *et al*[8] showed that the cancer-related rs6983267 SNP and its corresponding CCAT2 promoted myeloid cancers through certain SNP-specific RNA gene mutations. In 2019, Andersen *et al*[84] highlighted that the CCAT2 rs6983267 GG genotype was correlated with an elevated CRC risk, which was in agreement with the results of previous studies. In 2021, Yu *et al*[85] found that the rs6983267 G allele is related to a greater risk of lung cancer than the T allele. Structural predictions showed that rs6983267 affects the secondary structure of CCAT2, which is in line with the findings of Yu *et al*.[83] In addition, Thean *et al*[4] demonstrated a close relationship between the c-Myc expression in colon cancer and the metastasis time and the risk genotype of rs6983267 situated in CCAT2. From the above results, it is clear that the SNP associated with CCAT2 rs6983267 affects the occurrence and development of a variety of tumors, which may be achieved by affecting the transcription of the *Myc* gene, altering the structure of CCAT2, and altering the binding site of target miRNA.

Regulatory Mechanism of CCAT2

CCAT2 can participate in cell proliferation, migration, invasion, and other malignant processes by regulating ceRNAs, EMT, exosomes, signaling pathways, and interactions with other proteins. Refer to Table 2 for relevant information.

Clinical Significance of CCAT2

Role of CCAT2 as a biomarker for cancer diagnosis

Since its discovery, CCAT2 has been correlated with the incidence and progression of a variety of tumors. Furthermore, numerous studies have shown that it can be used as a new diagnostic biomarker, either alone or in combination with other molecules. Although the AUC value of CCAT2 is just 0.55, Wang *et al*[45] pointed out that it is still superior than traditional serum indicators such as AFP (AUC = 0.477), NSE (AUC = 0.424) and CA15-3 (AUC = 0.515). Zhang *et al*[87] investigated the five novel lncRNAs (LINC00857, BANCR, AOC4P, CCAT2, and TINCR) in the plasma of patients with CRC and found that when paired with Index I based on lncRNA, it outperforms Index II based on carcinoembryonic antigen (CEA) in distinguishing patients with GC from healthy controls. In the same year, Shaker *et al*[33] pointed out that serum CCAT2 can distinguish CRC patients from healthy controls, with sensitivity = 82.5%, specificity = 66.66%, and AUC = 0.73. Subsequently, Wang *et al*[43] found that compared with healthy controls, CCAT2 was remarkably overexpressed in the serum of CRC patients. The CCAT2 level after surgery was considerably lower in contrast with the level before surgery. Moreover, the researchers pointed out that CCAT2 was upregulated in CRC exosomes. Additionally, Gharib *et al*[5] designed a prediction panel based on ten significantly abnormally regulated lncRNAs, including CCAT2 in patients with CRC, and checked their expression in patients' stool. The following is a breakdown of the diagnostic accuracy of the panel in

Table 1: Functional characterizations of CCAT2 in multiple human cancers.

Tumor type	Dysfunction	Role	Role of function	Related genes and proteins	Related pathways	References
Osteosarcoma	Up	Oncogene	Proliferation↑, migration↑, invasion↑, cell cycle↑	c-Myc, miRNA143, miR-200b, N-cadherin, vimentin, E-cadherin, snail, LATS2, FOS–like antigen 2	PI3K/Akt signal pathy, AMPK signal pathy, GSK3β/β-catenin signal pathy	[31,34,56,57]
Neuroblastoma	Up	Oncogene	Cell viability↑, proliferation↑, migration↑, invasion↑, apoptosis↓			[1]
CRC	Up	Oncogene	Proliferation↑, apoptosis↓, migration↑, invasion↑, chromosome stability↓	c-Myc, miR-145, pre-miR-145, miR-21, miR-17-5p, miR-20a, BOP1, AURKB,	Wnt/β-catenin signal pathy	[6,7,41,44]
TC	Up	Oncogene	Proliferation↑, migration↑, invasion↑, apoptosis↓, cell cycle↑, chemotherapy resistance↑		Wnt/β-catenin signal pathy	[2,3]
Ovarian cancer	Up	Oncogene	Proliferation↑, migration↑, invasion↑, apoptosis↓, cell cycle↑, EMT↑	c-Myc, miR-424, TCF/LEF, MMP-7	Wnt/β-catenin signal pathy	[64-67,70]
Breast cancer	Up	Oncogene	Stemness↑, proliferation↑, migration↑, invasion↑, apoptosis↓, cell cycle↑, xenograft model↑, chemotherapy resistance↑	miR-205, Notch2, OCT4-PG1, OCT4, KLF4, CyclinD1, CyclinE1, CDK4, EZH2, p15, TGF-b, SMAD2, α-SMA	TGF-b signal pathy, Wnt/β-catenin signal pathy	[15-17,29,68,69]
Endometrial cancer	Up	Oncogene	Cell viability↑, migration↑, invasion↑, apoptosis↓	miR-216b	PTEN/PI3K/Akt signal pathy, mTOR signal pathy	[28]
Cervical cancer	Up	Oncogene	Proliferation↑, apoptosis↓, cell cycle↑			[62]
Nasopharyngeal carcinoma	Up	Oncogene	Proliferation↑, migration↑			[80]
PC	Up	Oncogene	Proliferation↑, migration↑, invasion↑, cell cycle↑, EMT↑	miRNA-217, TCF7L2	Wnt/β-catenin signal pathy	[73,74]
Lung cancer	Up	Oncogene	Cell viability↑, proliferation↑, migration↑, invasion↑, apoptosis↓, chemotherapy resistance↑, xenograft model↑, EMT↑	Pokemon, p21	Wnt/β-catenin signal pathy	[21-23,58-60]
Glioma	Up	Oncogene	Proliferation↑, migration↑, invasion↑, apoptosis↓, EMT↑, endothelial angiogenesis↑, apoptosis↓, cell cycle↑	miR-424, VEGFA, TGFβ, Bcl-2, Bax, caspase-3	PI3K/Akt signal pathy, Wnt/β-catenin signal pathy	[18-20,71,81]
HCC	Up	Oncogene	Proliferation↑, migration↑, invasion↑, EMT↑, apoptosis↓, xenograft model↑	FOXM1, NDRG1, miR-34a, miR-145, MDM2, p53/p21, SNAIL2, vimentin, E-cadherin		[27,48-51]
GC	Up	Oncogene	Cell viability↑, colony formation↑, migration↑, invasion↑, cell cycle↑, apoptosis↓, autophagy↑, EMT↑	P53, Caspase-8, PCNA, Bcl-2, p62, p-mTOR, p-Akt, LC3-II/LC3-I, p-p70S6K, POU5F1B, EZH2, E-cadherin, LATS2	mTOR signal pathy, PI3K/mTOR signal pathy,	[12-14,24]
Renal cell carcinoma	Up	Oncogene	Proliferation↑, invasion↑, apoptosis↓, xenograft model↑	miR-320a	Wnt/β-catenin signal pathy	[74,75]
AML	Up	Oncogene	Proliferation↑, cell cycle↑			[30]
EC	Up	Oncogene	Proliferation↑, migration↑, invasion↑,apoptosis↓, chemotherapy resistance↑, radiotherapy resistance↑	c-Myc, miR-145, p70S6K1, Akt, ERK, p70S6K1, p53, P21, Bax, APC, β-catenin, PCNA, cyclin D1	p53 signal pathy, Wnt/β-catenin signal pathy	[46,47]
CCA	Up	Oncogene	Proliferation↑, invasion↑, apoptosis↓, EMT↑			[53,54]
Pituitary tumor	Up	Oncogene	Proliferation↑, migration↑, invasion↑	PTTG1, SOX2, DLK1, MMP2, MMP13		[79]
Pancreatic ductal carcinoma	Up	Oncogene	Proliferation↑, invasion↑, xenograft model↑	KRAS	MEK/ERK signal pathy	[78]
OSCC	Up	Oncogene	Proliferation↑, migration↑, invasion↑, apoptosis↓	β-catenin, CCND1, c-Myc	Wnt/β-catenin signal pathy	[76,77]
Bladder Cancer	Up	Oncogene	Proliferation↑ migration↑, apoptosis↓			[25]

AML: Acute myeloid leukemia; AMPK: AMP-activated catalytic subunit alpha 1; AURKB: Aurora kinase B; BOP1: BOP1 ribosomal biogenesis factor; CCA: Cholangiocarcinoma; CCAT2: Colon cancer-associated transcript 2; CRC: colorectal cancer; DLK1: Delta like non-canonical Notch ligand 1; EMT: Epithelial-mesenchymal transition; EZH2: Enhancer of zest homolog 2; FOXM1: Forkhead box M1; GC: Gastric cancer; KLF4: Kruppel like factor 4; KRAS: KRAS proto-oncogene; LATS2: Large tumor suppressor kinase 2; mTOR: Mechanistic target of rapamycin; NDRG1: N-myc downstream regulated 1; OSCC: Oral squamous cell carcinoma; PC: Prostate cancer; PG1: polygalacturonase 1; PI3K: Phosphoinositide 3-kinase; PTTG1:Pituitary tumor-transforming gene 1; SOX2: SRY-box transcription factor 2; TC: Thyroid cancer; TCF/LEF: T-cell factor/lymph enhancer factor; TCF7L2: Transcription factor 7 like 2.

Table 2: Regulatory mechanism of CCAT2 in human cancers.

Regulatory mechanisms	Cancer types	Related molecules	References
ceRNA	Glioma	miR-424/VEGFA	[18]
	Osteosarcoma	miR-200b/VEGF; miR-143	[56,57]
	Endometrial cancer	miR-216b/Bcl-2	[28]
	Breast cancer	miR-205	[15]
	Overian cancer	miR-424/Notch2	[65]
	Hepatoocellular carcinoma	miR-34a/FOXM1; miR-145/MDM2	[27,50]
	PC	miR-217	[74]
	Renal cell carcinoma	miR-145/p70s6k1	[47]
	EC	miR-320a	[75]
	CRC	Pre-miR-145; miR-20a; miR-21; miR-17-5p; miR-145	[7,41]
EMT	PC	N-cadherin/Vimentin/E-cadherin	[73]
	GC	E-cadherin/Vimentin/N-cadherin/EZH2	[24]
	Hepatoocellular carcinoma	Vimentin/E-cadherin/SNAIL2	[49]
	Glioma	E-cadherin/Vimentin/N-cadherin/ Twist/β-catenin/Snail	[71]
	Ovarian cancer	E-cadherin/N-cadherin/Snail/Twist	[67]
	CCA	E-cadherin/Vimentin	[53]
Interaction with protein molecules	Breast cancer	EZH2/p15	[16]
	CRC	Myc/BOP1/AURKB	[6]
	Pituitary tumors	PTTG1/SOX2/DLK1/MMP2/MMP13	[79]
Signal pathway			
Wnt/β-catenin signal pathway	Lung cancer	β-catenin	[22]
	OSCC	β-catenin/Cyclin D1/Myc	[77]
	Renal cell carcinoma	β-catenin/c-Myc/Cyclin D1	[74]
	Ovarian cancer	β-catenin/c-Myc	[66,67]
	EC	β-catenin/Cyclin D1/c-Myc	[46]
	PC	β-catenin/Cyclin D1/c-Myc	[74]
	TC	β-catenin/c-Myc/Cyclin D1	[3]
	Breast cancer	β-catenin/Cyclin D1/c-Myc	[69]
	Glioma	β-catenin/c-Myc/CyclinD1	[20]
	Colon cancer	β-catenin	[7]
PI3K/Akt signal pathway	Endometrial cancer	PI3K/Akt/mTOR	[28]
	GC	PI3K/mTOR	[12,13]
	Osteosarcoma	PI3K/Akt	[56]
	Gliomas	PI3K/Akt	[18]
GSK3β/β-catenin signal pathway	Osteosarcoma	p-GSK3β/β-catenin	[86]
TGF-β signal pathway	Breast cancer	TGF-β/SMAD2/a-SMA	[17]
P53 signal pathway	EC	P53	[47]
	GC	P53	[12]
Exosomal pathway	Gliomas	VEGFA/TGF-β/Bcl-2/Bax/Caspase-3	[18,19]
	Nasopharyngeal carcinoma	–	[80]
Others	NSCLC	POKEMON	[60]
	HCC	NDRG1	[51]
	Osteosarcoma	LATS2; FOS like antigen 2	[31,57]

AURKB: Aurora kinase B; BOP1: BOP1 ribosomal biogenesis factor; CCA: Cholangiocarcinoma; CCAT2: Colon cancer-associated transcript 2; ceRNAs: Endogenous RNAs; CRC: colorectal cancer; DLK1: Delta like non-canonical Notch ligand 1; EC: Esophageal cancer; EMT: Epithelial-mesenchymal transition; EZH2: Enhancer of zest homolog 2; FOXM1: Forkhead box M1; GC: Gastric cancer; HCC: Hepatocellular carcinoma; LATS2: Large tumor suppressor kinase 2; MDM2: MDM2 proto-oncogene; mTOR: Mechanistic target of rapamycin; NDRG1: N-myc downstream regulated 1; NOTCH2: Notch receptor 2; NSCLC: Non-small cell lung cancer; OSCC: Oral squamous cell carcinoma; p70S6K1: Ribosomal protein S6 kinase, polypeptide 1; PC: Prostate cancer; PI3K: Phosphoinositide 3-kinase; POKEMON: Zinc finger and BTB domain containing 7A; PTTG1: Pituitary tumor-transforming gene 1; SMAD2: SMAD family member 2; SNAIL2: Snail family transcriptional repressor 2; SOX2: SRY-box transcription factor 2; TC: Thyroid cancer; VEGF: Vascular endothelial growth factor; VEGFA: Vascular endothelial growth factor A.

differentiating patients with CRC from healthy controls: AUC value in the training set was 0.8554, whereas the AUC value in the validation set was 0.8465. Among hematological malignancies, Shah *et al*[8] demonstrated the overexpression of CCAT2 in the peripheral blood and CD34(+) bone marrow cells of patients with MDS/MPN. In addition, Xu *et al*[72] discovered that the AUC of CCAT2 in the serum of patients with MM was 0.899; sensitivity was 85.80% and specificity was 83%. Moreover, the integration of CCAT2, β2-MG, HGB, and IgA was found to considerably improve the AUC value and sensitivity of MM diagnosis. In cervical cancer,

Wang *et al*[63] found that CCAT2, LINC01133, and LINC00511 were highly expressed in the serum of patients with CSCC. When these lncRNAs were combined with squamous cell carcinoma antigens, the AUC value was 0.94. In addition, the AUC value of the combined diagnostic model of CCAT2 and LINC01133 reached 0.894. Therefore, CCAT2 can be employed as a diagnostic indicator for malignant tumors such as CRC, ESCC, and cervical cancer, as evidenced by the above findings. Moreover, combining CCAT2 with other molecules can further improve the sensitivity and specificity of its diagnosis.

CCAT2's role as a prognostic biological marker for cancer

Increasing research reports have indicated that CCAT2 is significantly related to many prognostic indicators such as the tumor size, TNM stage, LNM, DM, vascular invasion, and OS. The findings of multivariate Cox analysis suggest that CCAT2 is an independent prognostic factor in malignancies such as neuroblastoma, CRC, cervical cancer, PC, HCC, GC, and CCA. This indicates that CCAT2 may be an ideal prognostic molecule. In neuroblastoma, the upregulation of CCAT2 affects tissue differentiation, tumor stage, and LNM.[1] In CRC, the high expression of CCAT2 is related to poor cell differentiation, deeper tumor invasion, LNM, advanced TNM stage DM, and vascular invasion. In contrast with patients exhibiting lower expression levels of CCAT2, those exhibiting elevated levels have been shown to have unfavorable disease-free survival and OS status.[32] Moreover, the combined expression of CCAT1, CCAT2, and CEA is an important determinant for effective prediction of recurrence-free survival in patients with stage II and stage III CRC.[88] The increased mRNA levels of *CCAT2* and *BOP1* in tumor tissues are correlated with a shortened survival duration in CRC patients.[6] Results of Kaplan-Meier survival analysis showed that patients with PC with elevated levels of CCAT2 expression exhibited unfavorable OS and PFS.[73] In lung cancer, CCAT2 overexpression is significantly related to lung adenocarcinoma ($P = 0.033$), and CCAT2 combined with CEA can predict LNM.[58] Moreover, elevated CCAT2 expression has been observed in SCLC tissues and cell lines, which is correlated with the malignant status and unfavorable prognosis of individuals suffering from SCLC.[59] In HCC, CCAT2 expression is considerably correlated with vascular invasion, histopathological grade, DM, as well as TNM stage. Results of Kaplan-Meier survival analysis illustrated that the HCC patients' OS duration in the group with high CCAT2 expression was remarkedly reduced as opposed to that in the group exhibiting low CCAT2 expression ($P = 0.016$).[52] Furthermore, elevated expression levels of CCAT2 is also correlated with unfavorable prognosis of patients with osteosarcoma,[31,34] renal cell carcinoma,[74] pituitary tumor,[79] ESCC,[26] breast cancer,[16] OSCC,[76,77] ovarian cancer,[64] glioma,[71] pancreatic ductal adenocarcinoma,[78] and bladder cancer.[25] Importantly, the abnormal expression of CCAT2 is also related to the capsular infiltration of TC,[2] FIGO stage of cervical cancer,[61] nerve infiltration of GC,[14,24] FLT3/ITD mutations, and polychromosomal karyotypes of AML,[30] and microvascular infiltration of CCA.[53,54] Taken together, CCAT2 is an ideal prognostic indicator in many tumor types.

Role of CCAT2 as a therapeutic target in cancer

In the last several decades, the biological functions and molecular mechanisms of CCAT2 have gradually been discovered. Several studies have suggested CCAT2 as a therapeutic target for cancer. Inhibiting the CCAT2 expression may suppress the proliferative, migratory, and invasive abilities of tumor cells, thus enhancing cell apoptosis and cell cycle arrest in CRC,[6] lung cancer,[21] neuroblastoma,[1] breast cancer,[69] CCA,[53] ovarian cancer,[64,65] and other tumors.[3,6,12,28,34,62,76,78] Furthermore, *in vivo* studies have shown that inhibiting the expression of CCAT2 can inhibit the growth of breast cancer,[69] HCC,[50] lung cancer,[21] and other cancer cells. In addition, Sun *et al*[18] pointed out that knocking out the expression of CCAT2 in glioma cells can significantly inhibit the growth and endothelial angiogenesis and also induce early glioma cells' apoptosis. Furthermore, suppressing the CCAT2 expression may boost the sensitivity of TC cells to Adriamycin and cisplatin,[2] breast cancer cells to tamoxifen,[29] lung cancer cells to cisplatin,[21] and increase the radiation effect of EC.[47] Calcitriol can suppress the ability of ovarian cancer cells to proliferate, migrate, and invade by means of the suppression of CCAT2 expression.[70] In HCC, UTMD-mediated siRNA targeting of CCAT2 significantly inhibited the growth of liver tumors in mice.[50] In bladder cancer, Li *et al*[25] constructed a tetracycline-induced double shRNAs vector for the purpose of regulating the dose-dependent induction of doxycycline based on the expression level of CCAT2. The synthetic "tetracycline" switch system could quantitatively regulate the CCAT2 expression in bladder cancer. Moreover, this system could respond to varying dosages of doxycycline to attenuate the proliferation of bladder cancer cells. Overall, both *in vivo* and *in vitro* trials have demonstrated the potential of CCAT2 in the treatment of malignant tumors. The clinical significance of CCAT2 can be seen in Table 3.

Conclusions

Research on CCAT2 for the last 10 years has yielded definite findings. However, there are several points worthy of an in-depth consideration: (1) Although many *in vivo* and *in vitro* studies have confirmed the abnormal expression of CCAT2 in tumor tissues, the results are not consistent[89-91]; (2) Most studies on CCAT2 have focused on common phenotypes and signaling pathways, and there are no studies on how CCAT2 regulates these phenotypes and its detailed mechanisms of action; (3) Although there have been reports about CCAT2 in *in vivo* experiments, the clinical value of CCAT2 needs to be established in future studies.

Taken together, CCAT2 is a potential diagnostic and prognostic indicator that can be used as a therapeutic target. However, more comprehensive studies are needed to establish the potential clinical value of lncRNA CCAT2.

Table 3: Clinical significance of CCAT2 in various human cancers.

Tumor type	sample	Dysfunction	Clinical significance	References
Osteosarcoma	Tissue: Tumor *vs.* normal	Up	Tumor size↑, tumor stage↑, OS↓	[34]
	Tumor tissue: High expression of CCAT2 *vs.* low expression of CCAT2	Up	DFS↓, OS↓	[31]
Neuroblastoma	Tumor tissue: High expression of CCAT2 *vs.* low expression of CCAT2	Up	3-year survival rate↓, tissue differentiation↓, tumor LNM stage↑, LNM↑	[1]
CRC	Tissue: Microsatellite stable colon cancer *vs.* adjacent normal	Up	Survival time↓, TNM stage↑, cell differentiation↓, tumor infiltration↑, LNM↑, DM↑, vascular infiltration↑, RFS↑, OS↑	[4,6,32,43,44,88]
	Stool: Cancer patients *vs.* healthy individuals	Up	Early detection indicators	[5]
	Cancer cell line: High expression of CCAT2 *vs.* low expression of CCAT2	Up	Chemotherapy resistance (5′FU and oxaliplatin) ↑	[6]
	Serum exosome: Cancer patients *vs.* healthy individuals	Up	Potential predictor	[43]
	Tissue: T variant of CCAT2 rs6983267 *vs.* G variant of CCAT2 rs6983267	Up	T variants reduce the risk of colon cancer by 30%;	[84]
	Tissue: High expression of CCAT2 *vs.* low expression of CCAT2	Up	DFS↓, OS↓	[32]
	Serum: Cancer patients *vs.* healthy people	Up	DFS↓, OS↓	[33]
	Serum: rs6983267 GG cancer patients *vs.* GT/TT cancer patients	Up	Non-invasive diagnostic biomarkers	[33]
TC	Tissue: Tumor *vs.* adjacent normal	Up	Tumor size↑, T stage↑, tumor metastasis stage↑, LNM↑, capsule infiltration↑	[2,3]
Cervical cancer	Serum: Tumor *vs.* normal	Up	Non-invasive biomarkers	[63]
Breast cancer	Tissue: Tumor *vs.* adjacent normal	Up	TNM stage↑, LNM↑, tumor metastasis↑, OS↓	[16,17]
	Tissue: Tumor *vs.* adjacent normal (pairing)	Up	DFS↓, OS↓	[68,69]
Ovarian cancer	Tissue: Tumor *vs.* adjacent normal	Up	FIGO stage↑, tumor grade↑, DM↑, prognostic biomarkers, OS↓, DFS↓	[64]
CSCC	Tissue: Tumor *vs.* adjacent normal	Up	Poor prognosis	[61]
PC	Tissue: Tumor *vs.* adjacent normal	Up	OS↓, PFS↓, independent prognostic indicators	[73]
Lung cancer	Tissue: Tumor *vs.* adjacent normal	Up	Malignant status, poor prognosis, CCAT2 combined with CEA can predict LNM	[58,59]
Glioma	Tissue: Tumor *vs.* adjacent normal	Up	Tumor size↑, tumor grade↑, clinical stage↑	[20,71]
	Tissue: High expression of CCAT2 *vs.* low expression of CCAT2	Up	Lifetime↓	[71]
HCC	Tissue: Tumor *vs.* adjacent normal	Up	Vascular infiltration↑, histopathological grade↑, DM↑, TNM stage↑, OS↓	[49,52]
GC	Tissue: Tumor *vs.* adjacent normal	Up	Tumor size↑, lymphatic metastasis↑, TNM stage↑, lymphatic invasion ↑, nerve invasion↑, DFS↓, OS↓, DM↑	[12,14,24,44]
Renal cell carcinoma	Tissue: Tumor *vs.* adjacent normal	Up	tumor size↑, tumor stage↑, OS↓	[74]
	Tissue: High expression of CCAT2 *vs.* low expression of CCAT2	Up	OS ↓	[74]
AML	tissue: High expression of CCAT2 *vs.* low expression of CCAT2	Up	OS↓	[30]
MM	Serum and bone marrow: Cancer patients *vs.* healthy individuals	Up	CCAT2, IgA, HGB, and β2-MG can significantly improve the sensitivity and AUC of MM diagnosis	[72]
EC	Tissue: Tumor *vs.* adjacent normal	Up	TNM stage↑, LNM↑, OS↓	[26]
CCA	Tissue: Tumor *vs.* adjacent normal	Up	Tumor size↑, microvascular infiltration↑, tumor (T)↑, lymph node (N)↑, metastasis (M)↑ and TNM overall stage↓, poor OS rate↓, PFS rate↓, tumor differentiation↑, postoperative recurrence↑	[53,54]
Pituitary tumor	Tissue: Tumor *vs.* adjacent normal	Up	Poor prognosis	[79]
Pancreatic CCA	Tissue: Tumor *vs.* adjacent normal	Up	Survival rate↓	[78]
OSCC	Tissue: Tumor *vs.* adjacent normal	Up	differentiation↓, T stage↓ and clinical stage↓	[76,77]
Bladder Cancer	Tissue: Tumor *vs.* adjacent normal	Up	Organization classification↑, TNM stage↑	[25]

β2-MG: Beta-2-microglobulin; 5′FU: 5-Fluorouracil; AML: Acute myeloid leukemia; CCA: Cholangiocarcinoma; CCAT2: Colon cancer-associated transcript 2; CEA: Carcinoembryonic antigen; CRC: Colorectal cancer; CSCC: Cervical squamous cell carcinoma; DFS: Disease-free survival; DM: Distant metastasis; EC: Esophageal cancer; FIGO: Federation International of Gynecology and Obstetrics; GC: Gastric cancer; HCC: hepatocellular carcinoma; HGB: Hemoglobin; LNM: Lymph node metastasis; MM: Multiple myeloma; OS: Overall survival; OSCC: Oral squamous cell carcinoma; PC: Prostate cancer; PFS: Progression-free survival; RFS: Recurrence-free survival; TC: Thyroid cancer.

Funding

This study was supported by the grant from Anhui Province Science Foundation (No. 2008085MH256).

Conflicts of interest

None.

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How to cite this article: Ma S, Wang W, Zhang D, Zhao G, Lu Z. Long non-coding RNA colon cancer-associated transcript 2: role and function in human cancers. Chin Med J 2022;135:2785–2797. doi: 10.1097/CM9.0000000000002286