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CCAT1: a pivotal oncogenic long non-coding RNA in human cancers

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Abstract

Long non-coding RNAs (lncRNAs) compose a group of non-protein-coding RNAs - more than 200 nucleotides in length. Recent studies have shown that lncRNAs play important roles in different cellular processes, including proliferation, differentiation, migration and invasion. Deregulation of lncRNAs has been widely reported in human tumours, in which they are able to function as either oncogenes (on the one hand) or tumour suppressor genes (on the other). Deregulation of CCAT1 (colon cancer–associated transcript-1), an oncogenic lncRNA, has been documented in different types of malignancy, such as gastric cancer, colorectal cancer and hepatocellular carcinoma. In this regard, enforced expression of CCAT1 exerts potent tumorigenic effects by promoting cell proliferation, invasion and migration. Recent evidence has also shown that CCAT1 may serve as a prognostic cancer biomarker. In this review, we provide an overview of current evidence relating to the role and biological function of CCAT1 in tumour development.

Introduction

Long non-coding RNAs (lncRNAs) consist of a group of non-coding RNAs with more than 200 nucleotides in length (1–4). These RNAs demonstrate limited protein-coding potential but could regulate gene expression transcriptionally and post-transcriptionally (5–7). Deregulation of lncRNAs has been observed in a variety of human diseases, including cancer (8–10). The functional involvement of lncRNAs in tumorigenesis has received much attention over the past decade (11–13). Pertinent to clinical practice, deregulation of lncRNAs in many cancer types has been associated with clinicopathological parameters, including metastasis, patients' survival and recurrence (6,14,15). lncRNA deregulation also contributes to cancer progression through abnormal regulation of genes involved in cancer-related cellular processes, including cell proliferation and invasion (12,16–24).

Colon cancer–associated transcript-1 (CCAT1) is a newly discovered lncRNA with 2628 base pairs in length (25–27). CCAT1 gene is located on chromosome 8q24.21 and in the vicinity of c-*MYC*, a well-known transcription factor (25,28). CCAT1 was first found to be upregulated in colon cancer (29). Recently, CCAT1 was found to be consistently deregulated in various cancer types (27,30,31). The location of CCAT1 gene on chromosome 8q24.21 is crucial as this area is a 'hot spot' harbouring multiple genetic alternations in both colon and prostate cancers (32).

CCAT1 is an enhancer-derived RNAs transcribed from a distal enhancer 515 kb upstream of the c-*MYC* gene (Fig. 1) (33,34). CCAT1 contains two exons and a poly-A tail and is mainly expressed in the nucleus. In colon cancer cells, CCAT1 is localized at its site of transcription (26,29), which is important for mediating the long-range chromatin interactions between *CCAT1* gene and *c-MYC* in conjunction with an enhancer 335 kb upstream of *c-MYC*. In this manner, CCAT1 transcriptionally activates c-*MYC* in a *cis*-acting manner. Depletion of CCAT-1 could, therefore, reduce the transcription of c-*MYC* gene.

In this review, we discuss the roles of CCAT1 as one of the most important regulatory RNAs in human cancer in relation to its deregulation, molecular functions and clinical significance (Table 1).

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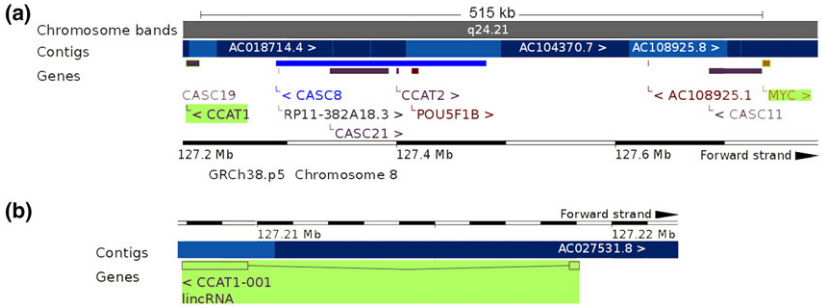

Figure 1. CCAT1 is an enhancer-derived RNAs transcribed from a distal enhancer 515 kb upstream of the c-*MYC* gene.

Colorectal cancer

Colorectal cancer is a common malignancy with around 1.2 million newly diagnosed cases worldwide each year (35–37). Its mortality rate is the third highest among all cancers, leading to approximately 0.6 million deaths annually (36,38,39). Currently, CEA and CA19-9 are the two most frequently used clinical diagnostic biomarkers (40–42). However, they have little significance in early diagnosis of colorectal cancer because of their lack of sensitivity and specificity. Identification, validation and clinical application of novel colorectal cancer-specific biomarkers may, therefore, improve the diagnostic accuracy, staging, patient follow-up and treatment selection of this prevalent disease.

Nissan *et al.* demonstrated that the expression level of CCAT1 was significantly upregulated in colon adenocarcinoma as compared with healthy controls (29). The expression of CCAT1 was significantly increased in both the early and late stages of colon cancer. CCAT1 was also strongly expressed in adenomatous polyps, tumour-proximal colonic epithelium, liver metastasis and the associated lymph nodes. Pertinent to non-invasive diagnosis, CCAT1 overexpression was detectable in 40% of peripheral blood samples of colorectal cancer patients, while it was largely undetectable in healthy controls. Alaiyan *et al.* also identified significant upregulation of CCAT1 in both pre-malignant and malignant lesions of the colon, including adenomatous polyps, primary tumour tissue, normal mucosa adjacent to primary tumour and lymph node, liver and peritoneal metastases (27).

In relation to prognostication, Ye *et al.* showed that the expression level of CCAT1 was significantly correlated with tumour staging, local infiltration depth, vascular invasion and CA19-9 level (43). CCAT1 also predicted the sensitivity of colon cancer cells to bromodomain and extraterminal (BET) inhibition, which preferentially reduced the growth of colon cancer with the CpG island methylator phenotype. In this regard, CCAT1 was sensitive to BET inhibition, correlated with c-*MYC* transcript and cell growth, and proposed to be a biomarker for selecting patients who are most likely to benefit from BET inhibitors (44). Another study investigated the diagnostic ability of a CCAT1-specific peptide nucleic acid-based molecular beacon (CCAT1 TO-PNA-MB) for detection of colorectal cancer (26). The data showed that CCAT1 TO-PNA-MB could serve as a diagnostic tool for colorectal cancer *in vitro*, *ex vivo* and *in situ* (human colon biopsies). Hybridization of TO-PNA-MB could detect CCAT1 expression in all (4/4) human colon biopsies with pre-cancerous adenomas, as well as in all (8/8) patients with invasive adenocarcinoma (penetrating the bowel wall). He *et al.* (45) further demonstrated that c-Myc could reciprocally increase CCAT1 expression through binding to its promoter region while overexpression of CCAT1 promoted colon cancer cell proliferation and

Table 1. Functional characterization of the CCAT1 in tumours

Cancer types	Expression	Phenotypes affected	Related gene	Role	References
Colorectal cancer	Upregulated	Proliferation, invasion	c-Myc	Oncogenic	(26,27,29,43–45)
Gastric cancer	Upregulated	Proliferation, invasion	c-Myc, ERK/MAPK	Oncogenic	(25,52,53)
Hepatocellular carcinoma	Upregulated	Proliferation, migration	let-7, HMGA2, c-Myc	Oncogenic	(28,30,65)
Gallbladder cancer	Upregulated	Proliferation, invasion	Bmi1, miR-218-5p	Oncogenic	(69)
Ovarian cancer	Upregulated	Metastasis		Oncogenic	(77)
Breast cancer	Upregulated			Oncogenic	(31)
Lung cancer	Upregulated	Proliferation		Oncogenic	(78,80)

invasion. To conclude, CCAT1 is a highly specific and readily detectable diagnostic biomarker for colorectal cancer, in which its upregulation contributes to both tumour growth and metastasis.

Gastric cancer

Gastric cancer is the fourth most frequent cancer and the second leading cause of cancer-related death worldwide (46–49). Although *Helicobacter pylori* and Epstein–Barr virus are two major aetiological factors of gastric cancer, our understanding of its molecular mechanisms remains largely incomplete (50–52). It is, therefore, crucial to identify novel molecular abnormalities in this deadly disease.

CCAT1 was upregulated in gastric carcinoma tissues compared with normal tissues (53,54). Similar to colorectal cancer, the transcription factor c-Myc increased the expression of CCAT1 by directly binding to its promoter region (25). The expression level of CCAT1 was correlated with cancer growth, lymph node metastasis and distal metastatic disease in gastric cancer. Moreover, CCAT1 promoted gastric cancer cell proliferation and migration *in vitro*. Mizrahi *et al.* also demonstrated that the expression level of CCAT1 was significantly higher in gastric cancer samples than that in the control group. In addition, CCAT1 expression was elevated in human gastric carcinoma cell lines. The expression levels of CCAT1 were found to be highest in tissues from recurrent gastric cancer cases (53). In conclusion, expression of CCAT1 is increased in gastric cancer, in which it serves as a potential marker for metastatic disease. Functionally, CCAT1 acts as an oncogene in gastric cancer, suggesting its potential utilization as a therapeutic target.

Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is the fifth most frequent solid tumour and the third leading cause of cancer deaths worldwide (55–58). Chronic infection with either hepatitis B or C virus plays significant roles in the development of HCC (59–61). Despite recent advances in surgery and medical treatment, the prognosis of HCC patients remains extremely poor (62–64). Therefore, it is crucial to understand the pathogenesis of HCC.

The expression level of CCAT1 was significantly elevated in HCC tissues compared with matched noncancerous hepatic tissues (28,30,65). In addition, the expression level of CCAT1 predicted poor prognosis in HCC, correlated with tumour size, microvascular invasion and alpha foetal protein (AFP) expression. Furthermore, CCAT1 promoted the proliferation and migration of HCC cells *in vitro* through binding and antagonizing let-7, a tumour-suppressive microRNA, and thereby derepressing the expression of let-7 targets HMGA2 and c-Myc. Taken together, CCAT1 is involved in the development and progression of HCC *via* functioning as a let-7 sponge. CCAT1 might act as an oncogene in HCC, suggesting its potential utilities as a prognostic marker and a therapeutic target.

Gallbladder cancer

Gallbladder cancer is fifth most frequent gastrointestinal malignancy (66–69). The pathogenesis of gallbladder carcinoma remains largely unknown. Therefore, it is of great importance to study its molecular mechanisms.

The expression of CCAT1 was higher in gallbladder cancer tissues compared with adjacent normal tissues (70). In addition, CCAT1 overexpression increased the expression of Bmi1, which is the target gene of miRNA-218-5p. Further analysis showed that CCAT1 knockdown inhibited the proliferation and invasiveness of gallbladder cancer cells, at least in part, through regulation of Bmi1. In this regard, transcript level of CCAT1 was correlated with Bmi1 in gallbladder cancer tissues. In conclusion, CCAT1 functions as an oncogenic lncRNA in gallbladder cancer in part through sponging miRNA-218-5p.

Ovarian cancer

Ovarian cancer is the most lethal gynaecological cancer and the fifth leading cause of cancer-related death (71–74). There has been no improvement in its mortality rate over the last 20 years (75–77). Much attention has, therefore, been given to the pathogenic mechanisms, particularly pathways that regulate metastasis of ovarian cancer.

Compared with the parental SKOV3 cells, the invasive ability of the SKOV3.ip1 cell line was significantly higher (78). Among 4956 detected lncRNAs in SKOV3.ip1 cells, the expression levels of 583 lncRNAs were upregulated and the expression levels of 578 were downregulated as compared with SKOV3 cells by microarray. Moreover, reverse transcription-quantitative PCR confirmed the deregulation of seven analysed lncRNAs (MALAT1, H19, UCA1, CCAT1, LOC645249, LOC100128881 and LOC100292680). These findings implicated that CCAT1 might play a role in ovarian cancer metastasis. Further studies are needed to determine the exact role of CCAT1 in ovarian cancer.

Breast cancer

Zhang *et al.* (31) demonstrated that the expression of CCAT1 was upregulated in breast cancer tissues compared with the adjacent normal tissues. The high

expression of CCAT1 was correlated with tumour–node–metastasis (TNM) staging, differentiation grade and lymph node metastases. Patients with high CCAT1 expression had a poor overall and progression-free survival. These results suggested that CCAT1 might function as an oncogenic lncRNA and serve as a potential prognostic marker in breast cancer.

Lung cancer

White *et al.* (79) depicted the landscape of lncRNA deregulation in lung cancer by integrative analysis of publicly available transcriptome sequencing data from 567 lung adenocarcinoma and squamous cell carcinoma tumours. By comparison with matched control, the authors identified 111 differentially expressed lncRNAs, including CCAT1. In a subsequent study, the same group demonstrated that knockdown of CCAT1 could potently inhibit lung cancer cell proliferation (80).

Conclusion

CCAT1 is a relatively well-characterized oncogenic lncRNA, which is upregulated in many types of cancer, including colorectal cancer, gastric cancer, HCC, gallbladder cancer, ovarian cancer, breast cancer and lung cancer. Functional characterization has also demonstrated that CCAT1 could promote tumour cell proliferation, migration and invasion. Although the involvement of c-Myc in the oncogenic function of CCAT1 has been demonstrated, its detailed upstream and downstream molecular mechanisms remain to be systematically studied. Pertinent to clinical utility, the overexpression of CCAT1 is very often associated with poor clinical outcomes. Therefore, this lncRNA may serve a prognostic biomarker. With more efforts being put forth to the study of lncRNAs especially CCAT1, it is hopeful that CCAT1 will obtain routine clinical utility at last.

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Conflict of interest

The authors declare no conflict of interest.

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