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Review

Colon cancer associated transcripts in human cancers

Yincong Chen[a,c,1], Haibiao Xie[a,b,1], Qunjun Gao[b,d,1], Hengji Zhan[b,1], Huizhong Xiao[e], Yifan Zou[a,b], Fuyou Zhang[b], Yuchen Liu[b,*], Jianfa Li[a,b,f,*]

[a] Shantou University Medical College, Shantou 515041, Guangdong Province, China
[b] Key Laboratory of Medical Reprogramming Technology, Shenzhen Second People's Hospital, First Affiliated Hospital of Shenzhen University, Shenzhen 518039, Guangdong Province, China
[c] Department of Pediatrics, Second Affiliated Hospital of Shantou University Medical College, Shantou 515041, China
[d] Guangzhou Medical University, Guangzhou 510182, China
[e] University of South China, Hengyang, Hunan 421001, China
[f] Guangdong and Shenzhen Key Laboratory of Male Reproductive Medicine and Genetics, Institute of Urology, Peking University Shenzhen Hospital, Shenzhen PKU-HKUST Medical Center, Shenzhen 518036, China

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ABSTRACT

Long non-coding RNAs serve as important regulators in complicated cellular activities, including cell differentiation, proliferation and death. Dysregulation of long non-coding RNAs occurs in the formation and progression of cancers. The family of colon cancer associated transcripts, long non-coding RNAs colon cancer associated transcript-1 and colon cancer associated transcript-2 are known as oncogenes involved in various cancers. Colon cancer associated transcript-1 is a novel lncRNA located in 8q24.2, and colon cancer associated transcript-2 maps to the 8q24.21 region encompassing rs6983267. Colon cancer associated transcripts have close associations with clinical characteristics, such as lymph node metastasis, high TNM stage and short overall survival. Knockdown of them can reverse the malignant phenotypes of cancer cells, including proliferation, migration, invasion and apoptosis. Moreover, they can increase the expression level of c-MYC and oncogenic microRNAs via activating a series of complex mechanisms. In brief, the family of colon cancer associated transcripts may serve as potential biomarkers or therapeutic targets for human cancers.

Contents

* Corresponding authors at: Key Laboratory of Medical Reprogramming Technology, Shenzhen Second People's Hospital, First Affiliated Hospital of Shenzhen University, Shenzhen 518039, Guangdong Province, China
E-mail addresses: liuyuchenmdcg@163.com (Y. Liu), lijianfayouxiang@163.com (J. Li).
[1] These authors have contributed equally to this work.

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1. Introduction

Long noncoding RNA (lncRNA) is known as a type of RNA molecules, more than 200 nucleotides in length, but lack of open reading frame (ORF) [1,2]. Therefore, lncRNAs can not be translated into proteins. However, they play important roles in the biological processes, including cell differentiation, gene regulation and chromatin remodeling [3–6]. In addition, lncRNAs are dysregulated in different cancers, promoting or inhibiting tumorigenesis and tumor progression [6–8]. According to the role of lncRNAs in cancers, the functional lncRNAs are classified into oncogenes or tumor suppressors. SPRY4-IT1, ATB, and HOTAIR are famous oncogenic lncRNAs, which can facilitate tumorigenesis [9–13]. Overexpression of oncogenic lncRNAs in normal epithelial cells may lead to carcinogenesis [14,15]. GAS5 and MEG3 are well-known tumor suppressor lncRNAs [16–18]. Dysregulation of tumor suppressor lncRNAs leads to tumor formation. Moreover, lncRNA regulates gene expression via affecting the process of chromatin modification, transcriptional regulation and post-transcriptional regulation [19–21]. Detailed signaling pathways were shown in Fig. 1.

The famous transcription factor c-MYC is overexpressed in various cancers, indicating a poor prognosis for cancer patients [22–24]. Mutation of c-MYC leads to chromosomal translocations and aberrant signal transduction, resulting in increased c-MYC expression and protein activity [25–27]. Moreover, c-MYC promotes the proliferation and growth of cancer cells via augmenting the expression of cancer-promoting genes [28–30]. Some lncRNAs are controlled by c-MYC, and lncRNAs can accelerate the cancer progression via up-regulating c-MYC expression. c-MYC is the upstream regulator of lncRNA PVT1, while amplification of PVT1 expression increases the expression of c-MYC [31,32]. LncRNA H19 expression is consistent with c-MYC expression, and c-MYC activates lncRNA H19 to promote cell proliferation [33,34]. In addition, C-MYC can regulate the biological response paths during the cancer development, including PI3K-Akt-mTOR pathway, Wnt/β-catenin signaling pathway and RAS/MAPK pathway [35–37].

Colon cancer associated transcript-1 (CCAT1) and colon cancer associated transcript-2 (CCAT2) are the members of the CCAT family and originally identified in the colon cancer tissues. CCAT1 is an enhancer-templated RNA, and it can modulate certain microRNAs expression to increase the expression of c-MYC reciprocally [38]. CCAT2 is located on the upstream of c-MYC, exerting its carcinogenic effects via regulating energy metabolism and activating the transcriptional activity of Wnt/β-catenin signaling [39,40]. A meta analysis related to CCAT2 demonstrated that overexpression of CCAT2 was positively correlated with the tumor stage, lymph node metastasis, and distant metastasis of cancer patients. High expression of CCAT2 can predict poor overall survival and progression-free survival for cancer patients [41]. These evidences demonstrated that CCATs are pervasively over-expressed in many cancers. They function as oncogenes in the process of tumor growth, progression and metastasis in vitro and in vivo. In this review, we summarized current knowledge of CCATs and focused on the characteristics and functions of CCATs.

2. Molecular characterizations of CCATs

CCAT1 maps to chromosome 8q24.2. There are two isoforms of CCAT1 in the genbank nucleotide sequence database. The long isoform of CCAT1 (CCAT1-L) is 5200nt in length and located on the 515 kb upstream of c-MYC. The short isoform of CCAT1 (CCAT1-S) is 2628 nt nucleotides in length, containing three short open reading frames corresponding to nucleotides: 95–208; 310–519 and 1621–1770. CCAT1-S contains 2 exons corresponding to nucleotides 1–288 and 289–2612 [42,43]. According to previous reports, CCAT1-L is only overexpressed in colon cancer [42], and CCAT1-S is highly expressed in colon cancer, gastric cancer (GC), gallbladder cancer (GBC), and hepatocellular cancer (HCC) [38,43–45]. CCAT1 serves as an enhancer-templated RNA for c-MYC. Importantly, inhibition of bromodomain and extraterminal (BET) can suppress CCAT1

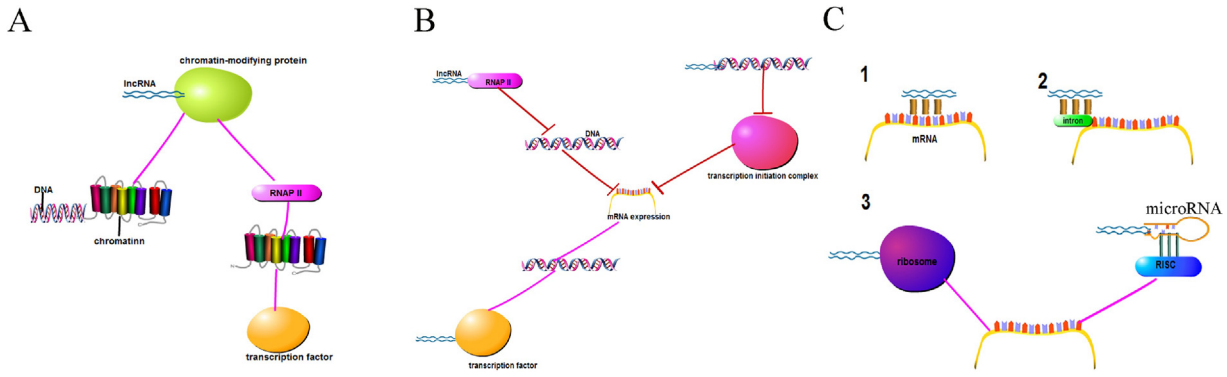

Fig. 1. LncRNA regulates gene expression via affecting the process of chromatin modification, transcriptional regulation and post-transcriptional regulation. A. LncRNA bounds to the chromatin-modification proteins to modifying the chromatin, which can edit the DNA fragment. LncRNAs bound to the chromatin-modification proteins to influence the activity of RNA polymerase II, which can regulate the transcription factor. B. Regulation of mRNA expression is controlled by RNA polymerase II, some transcription factors, and transcription initiation complex. And lncRNA interacts with RNA polymerase II or transcription initiation complex, which inhibits the mRNA expression. LncRNA binds to the transcription factor to control the mRNA expression. C. During the process of post-transcriptional regulation, lncRNA unites with the mRNA to form a double-stranded RNA complex to regulate gene expression. LncRNA combines with the intron of 5′ end of mRNA, preventing the intron from being split. Moreover, lncRNAs function as microRNA sponges to attract the microRNAs to form the RNA-induced silencing complex (RISC).