SNHG7 and *FAIM2* are up-regulated and co-expressed in colorectal adenocarcinoma tissues

SNHG7 a *FAIM2* jsou ve tkáni kolorektálního karcinomu up-regulovány a koexprimovány

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Summary

Background: The global incidence of colorectal cancer (CRC) is expected to be increased by 60% until a few years. Despite the advances in surgical and chemotherapy techniques, a significant proportion of patients with CRC have poor responses to treatments. These are the reasons that prove the importance of identifying molecular biomarkers as potential therapeutic targets. Long non-coding RNAs (lnc RNAs) participate in the initiation, development, progression, and metastasis of cancers such as CRC. Hence, this class of noncoding RNAs is known as biomarker for cancer diagnosis and prognosis. ***Materials and methods:*** In this experimental study, the extraction of total RNA from tissues, synthesis of complementary DNA as well as quantitative real-time polymerase chain reaction (qRT- PCR) were performed. Comparative cycle threshold method was applied to quantify the expression level of *lncRNA-SNHG7* and *FAIM2*. The relative amount of *lncRNA-SNHG7* and *FAIM2* was calculated using the equation $2^{-\Delta\Delta CT}$. ***Results:*** In this study, by qRT PCR, we concluded that the expression level of *SNHG7,* as a recently identified lncRNA and *FAIM2* were increased in colorectal cancer tissues compared with normal adjacent tissues. ***Conclusion:*** Our study indicates the potential importance of *SNHG7* and *FAIM2* expression for more studies in future.

Key words

lncRNA-SNHG7 – FAIM2 – colorectal cancer

Souhrn

Východiska: Očekává se, že během několika let celosvětově vzroste výskyt kolorektálního karcinomu (CRC) o 60 %. Přes pokroky v chirurgických technikách a v chemoterapii značná část pacientů s CRC vykazuje špatnou odpověď na léčbu. To jsou fakta, která svědčí o důležitosti identifikace molekulárních biomarkerů jakožto potenciálních léčebných cílů. Iniciace, růstu, progrese a metastazování nádorů, jako je např. CRC, se účastní dlouhé nekódující RNA (lnc RNA). Tato skupina nekódujících RNA je tedy známa jako biomarker pro diagnózu a prognózu tohoto nádorového onemocnění. ***Materiál a metody:*** V této experimentální studii byla provedena extrakce celkové RNA z tkání, syntéza komplementární DNA a kvantitativní polymerázová řetězová reakce v reálném čase (qRT-PCR). Pro kvantifikaci míry exprese lncRNA-*SNHG7* a *FAIM2* byla použita komparativní metoda „cycle threshold". Relativní množství lncRNA-*SNHG7* a *FAIM2* bylo vypočítáno pomocí vztahu $2^{-\Delta\Delta CT}$. ***Výsledky:*** Z výsledků qRT-PCR vyplynulo, že v porovnání s normálními tkáněmi bylo ve tkáni CRC zvýšené množství *SNHG7*, který byl jako lncRNA popsán teprve nedávno, a *FAIM2*. ***Závěr:*** Naše studie svědčí o potenciální důležitosti exprese SNHG7 and FAIM2 a o důležitosti provedení více studií v budoucnu.

Klíčová slova

lncRNA-SNHG7 – FAIM2 – kolorektální karcinom

Acknowledgments: The authors thank Shahid Chamran University of Ahvaz for supporting this study.

The authors declare they have no potential conflicts of interest concerning drugs, products, or services used in the study.

Autoři deklarují, že v souvislosti s předmětem studie nemají žádné komerční zájmy.

The Editorial Board declares that the manuscript met the ICMJE recommendation for biomedical papers.

Redakční rada potvrzuje, že rukopis práce splnil ICMJE kritéria pro publikace zasílané do biomedicínských časopisů.

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Submitted/Obdrženo: 1. 5. 2020
Accepted/Přijato: 16. 7. 2020

doi: 10.48095/ccko2020445

Introduction

The global burden of colorectal cancer (CRC) is expected to be increased, so that it is predicted that many new cases will be affected and many patients will die until the next decade. This increase in the number of patients and deaths is partly due to a lack of early diagnosis of this cancer [1,2]. Early high sensitive detection of the colon cancer can help to manage these patients. It would also improve the prognosis of this type of cancer and improve the recurrence risk [3,4]. Long noncoding RNAs (lncRNAs) are a class of non-coding RNA molecules with more than 200 nucleotides in length. They are located in nuclear or cytoplasmic compartments of the cell. They are usually transcribed by RNA polymerase II and conventionally cannot be translated into any proteins [5,6].

Evidence has shown that lncRNAs can participate in different cellular and molecular processes [7,8], including transcriptional regulation, cellular proliferation/differentiation and apoptosis, chromosome imprinting and remodeling, etc. [9].

It has been reported that several lncRNAs are involved in the pathogenesis of different diseases, including cancers. They can work as a tumor suppressor or onco lncRNAs in the initiation and progression of different cancers [10]. Thus, their dysregulation has been reported to be associated with the occurrence, development, progression, and metastasis in cancers [11,12] such as CRC. This class of noncoding RNAs is therefore known as biomarkers for cancer diagnosis and prognosis [9,13].

Long non-coding small nucleolar RNA host gene 7 (lncRNA *SNHG7*) is a member of recently identified lncRNAs which is located on 9q34.3 chromosome. Its potential role in several cancers including gastric cancer [14], breast cancer [15], hepatocellular carcinoma [10], glioblastoma, lymphoma, ovarian cancer [6,16], lung cancer [17,18], prostate cancer [19], and renal cell carcinoma [20] has been reported. Therefore, it can be considered as a promising candidate biomarkers for diagnosing colorectal cancer. Hence, previous studies have suggested that *SNHG7* may be a potential molecule for the diagnosis and treatment of different cancer types.

While the dysregulated expression of *SNHG7* has been reported in several cancer cell lines and tumors, there is a little information about the role of *SNHG7* in colorectal cancer. Thus, we investigated the expression level of *SNHG7* in colorectal adenocarcinoma tissues compared with adjacent normal tissues. In the current study, we demonstrated that *lncRNA-SNHG7* was aberrantly up-regulated in colorectal adenocarcinoma tissues. Furthermore, we found a correlation between the expression levels of this lncRNA with the expression of *FAIM2* as an anti-apoptotic gene. So, our study confirms a potential role of *SNHG7* in colorectal cancer and highlights its role in the initiation/progression of colorectal cancer.

Tab. 1. The clinicopathological factors of 25 patients.

Clinical factors	Number of cases	% of patients
Gender		
male	13	52
female	12	48
Age		
< 60 years	15	60
≥ 60 years	10	40
Histological grade		
low	7	28
middle or high	18	72
Tumor invasion depth		
T1–T2	6	24
T3–T4	19	76
Lymph node metastasis		
N0	12	48
N1–N2	13	52
TNM stage		
I–II	12	48
III–IV	13	52
Total	25	100

Materials and methods

Patients and tissues collection

This study was ethically approved by Shahid Chamran University of Ahvaz. The colorectal tumoral and non-tumoral tissue samples were obtained from Iran Tumor Bank (Tehran, Iran). Totally, 25 paired tissue samples were examined for gene expression (25 colorectal cancer tissues and 25 normal adjacent tissues).

The diagnosis of all patients with CRC was histopathologically confirmed by the Tumor Bank. Distant metastasis and histological differentiation were classified according to the standard criteria. The clinical stage was evaluated on the basis of the Union for International Cancer Control (UICC) TNM classification system.

The clinicopathological characteristics of the patients are summarized in Tab. 1.

The tumor tissues and paired adjacent normal tissues were immediately frozen in liquid nitrogen and stored at –80 °C for further experiments.

RNA preparation, cDNA synthesis, and quantitative real-time PCR

Total RNA from tissues was extracted by using RNX™-plus reagent (CinnaGen, Iran) according to the protocol of the manufacturer. The concentration of precipitated RNAs was measured by a NanoDrop 2000 spectrophotometer RNA (Thermo Fisher Scientific, Waltham, USA) and the quality was evaluated by agarose gel electrophoresis.

Complementary DNA (cDNA) was synthesized from 1.5 µg total RNA using random hexamer and oligo (dT) primers through a synthesis kit (Takara, Shiga, Japan) in a total 10 µL reaction mixture, according to the manufacturer's instructions.

The quantitative real-time PCR (qRT PCR) assays were performed using SYBR Green (Takara, Dalian, China) on the Applied Biosystems StepOne Real-time PCR System (Applied Biosystems, Foster City, USA) with suitable controls. All reactions were run in duplicate and the comparative cycle threshold (CT) method was applied to quantify the expression level of *lncRNA-SNHG7* and *FAIM2*.

The results were normalized to the expression of glyceraldehyde-3-phos-

phate dehydrogenase (GAPDH). The PCR primers were designed and analyzed by Oligo 7 and Gene Runner software. The primer sequences used for the studies are shown in Tab. 2. The relative amount of *lncRNA-SNHG7* and *FAIM2* was calculated using the equation $2^{-\Delta\Delta CT}$.

Statistical analysis

The data were used for statistical analysis by GraphPad Prism 5. The t-test was used for the statistical analysis of the data. The significance was considered at the level of $P < 0.05$. In addition, the relationship between gene expression changes was determined using Pearson correlation coefficient.

Tab. 2. Sequence of primers for *GAPDH*, *SNHG7* and *FAIM2* genes.

Gene	RefSeq	Sequence of primer
GAPDH	NM_002046	Forward: 5'-GTGAACCATGAGAAGTATGA-3'
		Reverse: 5'-CATGAGTCCTTCCACGATAC-3'
SNHG7	NR_003672	Forward: 5'-TGGTGTGTCCCTTGGTGGAGA-3'
		Reverse:5'-GGGCTTAGTTACATTGGAGGATTGA-3'
FAIM2	NM_012306	Forward: 5'-GGCGTGCTCTTCGTGCTTC-3'
		Reverse: 5'-TGGCGTCGGTTACCCATCA-3'

Results

SNHG7 was highly expressed in CRC tissues

We performed qRT-PCR in order to detect the relative expression of *SNHG7* in CRC tumor tissues and normal adjacent tissues. The results showed that the expression of *SNHG7* is increased in the tumor samples in comparison with normal tissues (fold change 3.491; $P = 0.024$) (Fig. 1A).

FAIM2 expression was increased in tumor samples compared to normal tissues

The *FAIM2* gene in the tumor samples showed a higher expression compared with the normal tissues (fold change 4.395; $P = 0.0396$). The following diagram illustrates this comparison statement (Fig. 1B).

Positive correlation between the *FAIM2* and *SNHG7* expression

The relationship between genes expression changes was determined in GraphPad Prism 5 using Pearson correlation coefficient ($P < 0.0001$, correlation coefficient = 0.7027). The model shows the correlation between changes in the expression of *FAIM2* and *SNHG7* genes (Fig. 1C).

Correlation of *SNHG7* and *FAIM2* expression with clinicopathological features of CRC patients

In addition to previous results, the correlation of *SNHG7* and *FAIM2* expression with clinicopathological characteristics of colorectal cancer samples was analyzed by t-test.

In this study, the relationship between tumor stages and grades, lymph node invasion and tumor location for both genes were examined. The increase in the expression of *FAIM2* and *SNHG7* genes was associated with high stages of cancer (III–IV) and metastasis to lymph nodes (N1–N2), although these relationships were not significant. The increase in the expression of *SNHG7* was also correlated with high tumor grades (II–III) (Fig. 2).

Discussion

Colorectal cancer is the third most commonly diagnosed cancer in males and the second one in females worldwide [21]. Although surgery is an effective way for removing the primary tumor, many patients are diagnosed with metastases after this primary surgery. Despite the advances in chemotherapy and surgical methods, a significant number of patients with CRC have poor responses to treatments. A suitable biomarker or biomarker panel along with colonoscopic method would help screening and improving the diagnosis protocols [22].

Long noncoding RNAs (lncRNAs) are a type of non-coding RNA molecules which are longer than 200 nucleo-

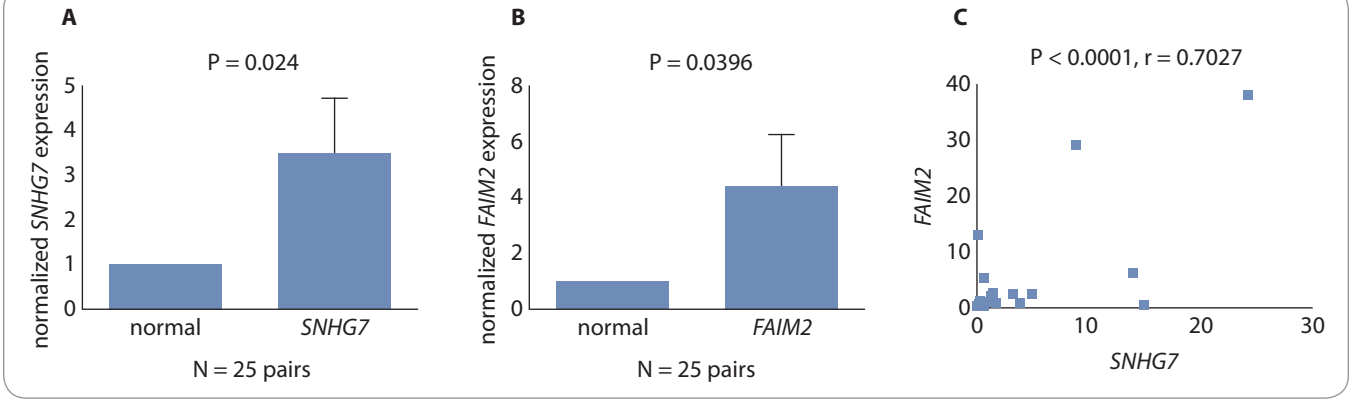

Fig. 1. Comparison between normalized expression levels of the desired genes. A) SNHG7 was highly expressed in CRC tissues compared with adjacent normal tissues. B) The *FAIM2* gene in the tumor samples showed a higher expression than the normal tissues. C) Change in the expression of *FAIM2* and SNHG7 genes indicated a positive correlation between their expression levels.

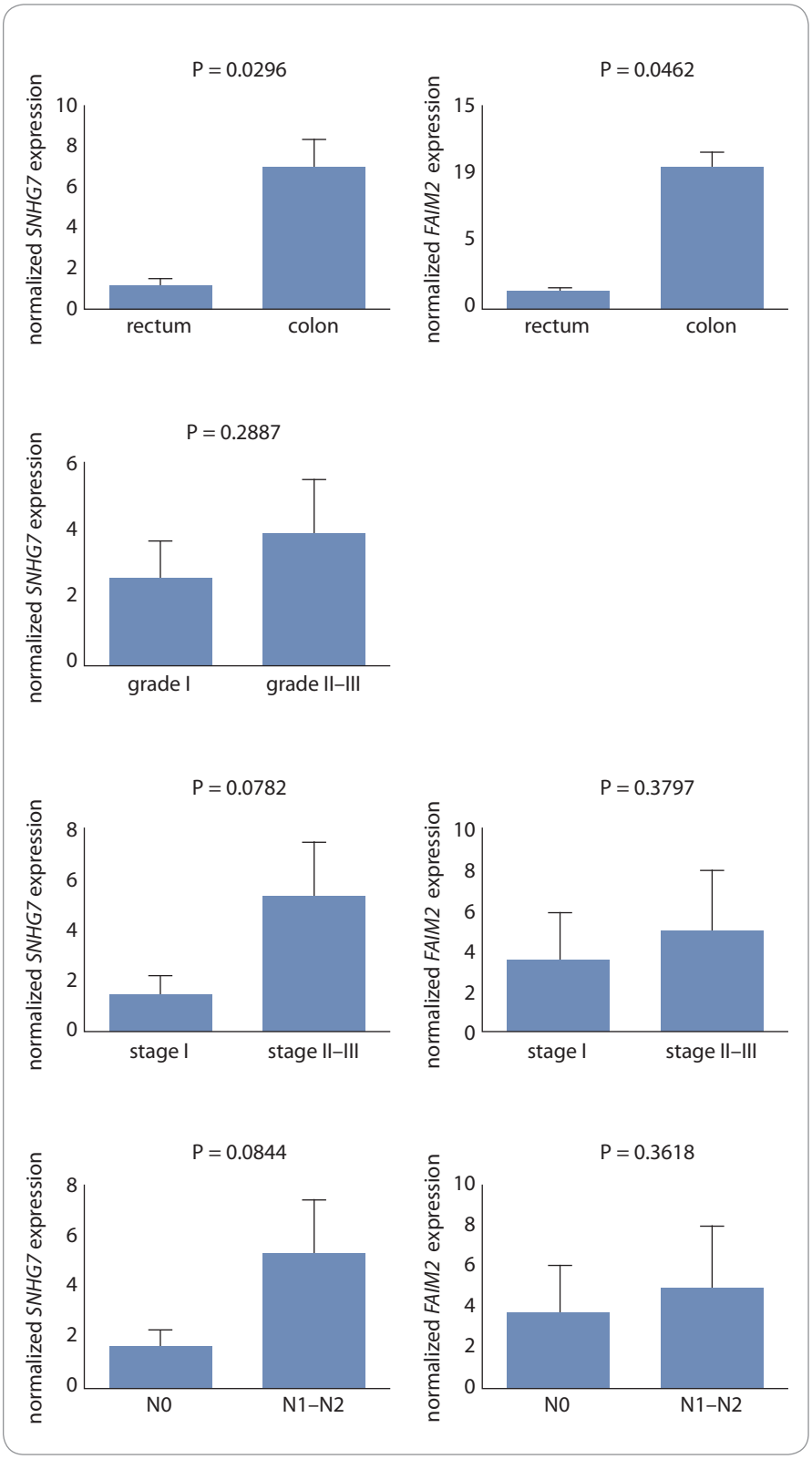

Fig. 2. The high expression level of *FAIM2* and *SNHG7* genes was associated with high stages of cancer (stage III–IV) and metastasis to lymph nodes (N1–N2). Increasing the expression of *SNHG7* also correlated with high tumor grades, although these relationships were not significant. The expression rate of *SNHG7* in the colon was higher than the rectum with P = 0.0296, also over expression of *FAIM2* correlated with colon with P = 0.0462.

tides and do not have any open reading frame. They participate in many biological processes in different levels and compartments [23–25].

However, researchers have found that lncRNAs exhibit critical roles in the development of many diseases with complicated mechanism, such as tumor [26]. In fact, lncRNAs participate in the occurrence and progression of metastasis of different cancers such as CRC. This class of non-coding RNAs is therefore known as potential biomarkers for cancer diagnosis and prognosis.

The Small Nucleolar Host Gene (*SNHG*) is a gene family with more than 10 members. Their potential role in tumor progression has been investigated in recent years. However, their functional mechanism in cancers has not been diagnosed yet. As an example, *SNHG*1, a potential oncogene, is over-expressed in colorectal cancer. It induces cell proliferation by sponging a microRNA named miR-145, and has a correlation with poor prognosis of CRC [27,28]. The RNA acts via Wnt/β-catenin signaling pathway, and may significantly be associated with the development and progression of this cancer [29,30].

In this study, the expression level of another member of this family called *SNHG7* and its potential collaborative gene called *FAIM2* were investigated in colorectal cancer. *FAIM2* is a gene encoding the *FAIM2* protein that plays a role in the Fas signaling pathway [17,31].

In recent years, changes in lncRNA-*SNHG7* expression have been reported in hepatocellular carcinoma [10], glioblastoma [6,16], gastric cancer [14], breast cancer [15], lung cancer [17,18], prostate cancer [19], and renal cell carcinoma [20]. High levels of *SNHG7* expression are involved in cell proliferation, migration, invasion, lymph node metastases as well as in TNM stage. On the other hand, increased level of *SNHG7* expression inhibits apoptosis and negatively correlates with the prognosis and survival rate of patients with various cancers.

She et al [17,18] found that the changes in the expression of *SNHG7* and *FAIM2* can be found in lung cancer. Their results showed that the expression level of *FAIM2* and *SNHG7* are up-regulated in

lung cancer tissue. It was found that the expression of *lncRNA-SNHG7* had a positive association with *FAIM2* in this type of cancer. They knock down the *lncRNA-SNHG7* and *FAIM2* by siRNA which inhibits proliferation, cell migration, and invasion; and it also induces apoptosis.

Studies have shown that the *FAIM2* gene is involved in the Fas signaling pathway, which is an apoptotic pathway. This gene produces a membrane protein called Fas apoptotic inhibitory molecule 2 (*FAIM2*), which is considered as an anti-apoptotic protein and a member of the lifeguard (LFG) family [18]. In the Fas signaling pathway, binding of the Fas receptor (CD95) to FasL (Fas Ligand) on the surface of the other cells can induce apoptosis signaling [31,32].

In this study, we recognized a significant increase in the expression of *lncRNA-SNHG7* in tumor tissues compared with normal adjacent tissues (P = 0.024) by checking 25 patients with CRC. The expression of *FAIM2* was also found to be increased in tumor tissues compared with normal tissues (P = 0.0396). To our knowledge, this study is the first one reporting the over-expression of *FAIM2* as well as its correlation with *SNHG7* in colorectal cancer. During the processing of the current study and manuscript, there were published two relevant studies which also showed the over-expression of *SNHG7* in colorectal cancer [33,34]. In the current study, we investigated the possible relationship between the changes of *SNHG7* and *FAIM2* expression in colorectal cancer for the first time. We found that the correlation coefficient was positive and equal to 0.7027, which indicates a positive relationship between the expressions of these two genes. This correlation indicates a potential correlation between the roles of these molecules in colorectal cancer. The results are consistent with the previous study [18] which showed this correlation.

Based on the results of this study as well as on the results of previous reports, it can be argued that *SNHG7* and *FAIM2* probably collaborate for colorectal cancer progression.

Conclusion

In summary, our data demonstrate that abnormal expression of *SNHG7* and *FAIM2* and their correlation may play important roles in CRC and may serve as a target for diagnosis and therapy of colorectal cancer. Our results suggest further *in vitro* and *in vivo* studies to reveal their role in oncogenesis.

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