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SIRT1 and Lnc-OC1 Expression in Breast and Colorectal Cancers

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Abstract

Abstract

***Background*:** The SIRT1 gene is involved in many physiological activities of the body, including inflammation, innate and acquired immune system responses, neurodegeneration, age-related disorders, life-span extension, obesity, and heart disease. But its role in cancer is not yet fully understood. Considering the possible role of Lnc-OC1 in the regulation of SIRT1 and tumorigenesis, this study was designed and performed to evaluate the expression of SIRT1 and Lnc-OC1 genes in patients with breast and colorectal cancer.

***Methods*:** In this case-control study, during September 2018 to July 2021, 84 patients (47.61%≤60 years, 52.38 >60 years) with breast cancer and 59 patients (42.37% ≤ 60 years, 57.62> 60 years) with colorectal cancer confirmed by pathological findings and the expression of SIRT1 and Lnc-OC1 were assessed using Quantitative real-time PCR.

***Results*:** In colorectal cancer, it appears that increasing the expression of Lnc-OC1, decreased the expression of SIRT1. The expression of Lnc-OC1 gene in patients with breast and colorectal cancer has increased compared to normal tissue. The expression of SIRT1 in patients with breast cancer increased significantly compared to normal tissues, but decreased in patients with colorectal cancer.

***Conclusion*:** The results showed that Lnc-OC1 could be used as an early diagnosis for colorectal cancer by reducing SIRT expression, and the expression of these two genes could be used to assess the prognosis for breast cancer.

Keywords: SIRT1, Lnc-OC1, Breast cancer, Colorectal Cancers

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Introduction

Breast cancer is the most common cancer among women worldwide and the second leading cause of cancer death in women, after lung cancer. It accounts for 23% of all cancers worldwide and 14% of all cancer deaths(1, 2). One million new cases of the disease are annually diagnosed worldwide(3). Colorectal cancer is one of the most common cancers in the world, being the third most common cancer in men and the second most common cancer in women. According to the World Health Organization in 2018, 861,000 people died of colorectal cancer(4).

Cancer is a multifactorial disease in which genetic and environmental factors play an important role. Although known hormonal factors and lifestyle play an important role in cancer, but family history is one of the most important risk factors for the disease(5). The risk of breast cancer in women with a history of the disease in first-degree family members is 1-2 times higher than in those with no family history(6). In recent years, molecular diagnostic methods, including the study of multigene expression, have been widely used to better manage breast cancer using clinical data and histopathological results. With the use of new molecular methods, it is possible to identify many regions in the genome that undergo changes, both at the chromosomal level and at the DNA level (7).

Cancer is based on genetic disorders. For this reason, today a very important role in this category of diseases is considered for it. These abnormalities can be large (at the molecular scale) at the chromosome level or very small at the nucleotide level, leading to irreversible changes in the cell. Family screenings we can help diagnose the disease or assess the likelihood of recurrence, response to treatment, and predict the prognosis of cancer(8, 9).

LncRNAs as non-coding RNAs are with more than 200 nucleotides in length. In recent years indicated that these RNA fragments react through specific sequences with the regions that regulate gene transcription and involving in regulating more than 80% of the human genome(10, 11). LncRNA controls various cellular processes including transcription, translation, chromatin alterations, cell cycle, cell differentiation, oncogene signaling pathways, and cancer suppressor genes. For this reason, in recent years, the different roles of lnc-RNA in complex human diseases such as cancer have been extensively investigated (12). In recent years, a new competitive lnc-RNA androgen called Lnc-OC1 has been identified that can bind to miR-34a/c to suppress the tumor suppression effects of miR-34a/c which can act as an oncogene and lead to the development and progression of cancer (13). In a completely opposite study, it appeared that Lnc-OC1 increases in ovarian cancer and can inhibit cell proliferation, colony formation, invasion and migration, and ultimately prevent tumorigenesis (14). In another study, LncRNA showed that can stimulate triple-negative breast cancer by downregulating miR-34a (15).

The SIRT1 gene expresses an NAD-dependent deacetylase protein called sirtuins, which has conflicting data regarding its role as an oncogene or tumor suppressor gene. On the one hand, the expression of this gene increases in tumors and cancer cell lines, which is associated with inhibition of apoptosis and reduced expression of tumor suppressor genes such as P53, FOXOs, and nuclear factor Kappa B (NFkB) and therefore introduced as an oncogene(16). On the other hand, it acts as an apoptosis and inhibitor of cell proliferation and thus exhibits tumor suppressor behavior. In general, sirtuin regulates the process of apoptosis in response to

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oxidative and genotoxic stress(17). For example, in 2019, stated that due to its anti-apoptotic function, this gene may play a role in the prevalence of cancer in humans(18). In another study, it was found that SIRT1 prevents cancer metastasis and plays a role by negatively regulating miR-15b-5b expression(19). Considering the role of Lnc-OC1 in inhibiting miR-34a/c and subsequent tumorigenesis and regulation of SIRT1 gene expression by miR-34a this study is aimed to assess the expression of Lnc-OC1 and SIRT1 genes in colorectal cancer and breast cancer tumor tissue in different grades and compare to healthy tissues.

Methods

In this case-control study, during September 2018 to July 2021, 84 patients with breast cancer and 59 patients with colorectal cancer confirmed by pathological findings referred to Imam Khomeini Hospital, Tehran, Iran. Among 84 patients with breast cancer, 23, 16, 20, 12 and 13 patients were in grade I to V, respectively and among 59 patients with colorectal cancer, 17, 14, 12 and 16 patients were in grade I to IV, respectively. All of the cases were rechecked and reclassified based on the criteria of the WHO categorization. All samples were placed in 1.5 ml micro tubes with RNAlater Stabilization Solution (Qiagen, Germany) and frozen at -20 ° C. This investigation is ethically approved by ethic committee of Imam Khomeini Hospital. The processes of the study were described for all patients and their companions, and informed consent (according to the Declaration of Helsinki) was completed by all patients. The patients with colorectal cancer were categorized based on their age, sex, serum CA19-9 levels, serum carcinoembryonic antigen (CEA) levels and stage (I, II, III and IV). The patients with breast cancer were classified into 5 groups according to the based on estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and Ki-67 proliferative file, along these lines: grpou I: ER^+, PR^+, $HER2^-$ and Ki-67 <14%, group II: ER^+, PR^+, $HER2^-$ and Ki-67 >14%, group III: ER^+, PR^+, $HER2^+$, group IV: ER^-, PR^- and HER2 overexpressed and group V: ER-, PR- and $HER2^-$ (Triple-negative breast cancer (TNBC).

RNA extraction and cDNA synthesis

One hundred g of each paraffin tissue sample was used to extract RNA, which was prepared by microtome with 10 micron slices of tissue. For deparaffinization and extraction, RNA Tri-pure Isolation Reagent solution (Roche, Germany) was used and the concentration and purity of the extracted RNA were measured in a Thermo Scientific NanoDrop and the optical density was measured at 260 nm and 280 nm of wavelengths. For synthesis of cDNA, 1µg of each sample was treated with DNaseI enzyme (ThermoScientific, USA) to remove any genomic DNA contamination, and 1 µg of total RNA treated with reverse transcriptase enzyme and hexamer random primer, cDNA (Fermentas, Canada) was made (20).

NAFLD and biochemical assessments

A skilled radiologist performed the abdominal ultrasound. Images were assessed again by a gastro-intestine-hepatologist. The Hamaguchi score assessing hepatic steatosis by hepatorenal echo contrast, bright liver, and vessel blurring was used to diagnose NAFLD (14, 18).

Blood specimens were drawn between 8 and 10 AM after at least 8 hours of fasting. Obtained samples were sent to the Firoozgar Hospital's laboratory, and the analyses were performed using the Free Testosterone AccuBind ELISA Kit-96 wells (Monobind Inc ®, USA). Also, aspartate aminotransferase (AST),

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alanine transaminase (ALT), triglyceride (TG), cholesterol, high-density lipoprotein (HDL), low-

Quantitative real-time PCR

Primers was designed using Primer Express software, version 3 (Applied Biosystems, Austin, TX, USA) as an exon-exon junction. Also, in order to check the accuracy of the primers, it was checked on BLAST. The binding temperatures of the target gene primers and the internal control were closely designed. The sequence of designed primers is as follows: Polymerase chain reaction in a total volume of 25 µl including: 100 ng Master Mix 2X and ROX50X cDNA, 10 picomoles of specific primer of each gene with conditions of 10 min at 94 ° C, 15 s at 95 ° C, 20 s at 61.5, 62 and 58 ° C for SIRT1, Lnc OC1 and GAPDH genes, respectively and 30 s were performed at 35 ° C in 35 cycles (21).

Statistics

Ethical Statement

The processes of the study were described for all patients and their companions, and informed consent (according to the Declaration of Helsinki) was completed by all patients.

Statistical analysis

SPSS 21.1 (SPSS Inc, Chicago, IL, USA) software was used for statistical analysis. Student T test was used to evaluate the significant level of difference in gene expression between tumor and non-tumor samples. Independent-sample T test and One-way ANOVA were used to examine the correlation between changes in gene expression and pathological indices of patients. The Pearson test to examine the correlation between changes in expression of genes studied and pathological indices of patients.

Results

In this study, quantitative Real-Time PCR technique and $2^{-\Delta\Delta ct}$ method were used to measure the expression level of SIRT1 and Lnc-OC1 genes in patients with breast and colorectal cancer. The expression of GAPDH gene was used as a control to normalize expression changes. The clinico-pathological characteristics in patients with breast and colorectal cancer were mentioned in tables 2 and 3, respectively. The results of Pearson correlation test showed that the expression of genes SIRT1 and Lnc-OC1 in patients with breast cancer had no significant relationship with age (P=0.126), tumor size (P=0.094) and metastases (P=0.117). Using Shapiro Wilk test, it was found that the distribution of data in this study was not normal and therefore mann-whitney test was used to compare the expression of these genes in tumor tissue and normal tissue.

Table 1. The Primers sequences of SIRT1, Lnc-OC1 and GAPDH genes.

Primers		Sequences 5’-3’
SIRT1	Forward	TAATTCCAAGTTCCATACC
	Reverse	ATTCACCACCTAAACCTAT
Lnc-OC1	Forward	TAGTAGTAACACAGTAGCCTAT
	Reverse	AACACAGAGCAGATATTGG
GAPDH	Forward	CCACTCCTCCACCTTTGACG
	Reverse	CCACCACCCTGTTGCTGTAG

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Table 2. Clinico-pathological characteristics of the patients with breast cancer in different grades

Characteristics		Total	Groups					P-value
			Group I	Group II	Group III	Group IV	Group V	
		N= 84 (%)	N= 23 (%)	N= 16 (%)	N= 20 (%)	N= 12 (%)	N= 13 (%)	0.001
Age	≤60	40 (47.61)	9 (39.13)	9 (56.25)	10 (50.00)	6 (50.00)	6 (46.15)	0.001
	>60	44 (52.38)	14 (60.86)	7 (43.75)	10 (50.00)	6 (50.00)	7 (53.84)	
Size (cm)	≤1.5	23 (27.38)	6 (26.06)	4 (25.00)	6 (30.00)	3 (25.00)	4 (30.76)	0.001
	1.5 - 2.5	33 (27.38)	9 (39.13)	7 (43.75)	7 (35.00)	5 (41.66)	5 (38.46)	
	>2.5	28 (45.23)	8 (34.78)	5 (31.25)	7 (35.00)	4 (33.33)	4 (30.76)	
ER	Positive	51 (60.71)	15 (65.21)	9 (56.25)	12 (60.00)	7 (58.33)	8 (61.53)	0.001
	Negative	33 (39.28)	8 (34.78)	7 (43.75)	8 (40.00)	5 (41.66)	5 (38.46)	
PR	Positive	30 (35.71)	16 (69.56)	11 (68.75)	2 (10.00)	0 (0.00)	1 (7.69)	0.001
	Negative	54 (64.28)	7 (30.43)	5 (31.25)	18 (90.00)	12 (100.0)	12 (92.30)	
HER2	Positive	34 (40.47)	4 (17.39)	2 (12.5)	16 (80.00)	10 (83.33)	2 (15.38)	0.001
	Negative	50 (59.52)	19 (82.60)	14 (87.5)	4 (20.00)	2 (16.66)	11 (84.61)	
Ki-67	≤20%	32 (38.09)	20 (86.95)	5 (31.25)	6 (30.00)	1 (8.33)	0 (0.00)	0.001
	>20%	52 (61.90)	3 (13.04)	11 (68.75)	14 (70.00)	11 (91.66)	13 (100.0)	

ER: Estrogen Receptor, PR: Progesterone Receptor, HER2: Human Epidermal growth factor Receptor 2, Ki-67: cellular marker for proliferation.

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Table 3. The expression of SIRT1 gene in patients with colorectal cancer in different grades

Characteristics		Total	Groups				P-value
			Group I	Group II	Group III	Group IV	
		N= 59 (%)	N= 17 (%)	N= 14 (%)	N= 12 (%)	N= 16 (%)	
Gender	Male	38 (64.4)	12 (70.58)	8 (57.14)	8 (66.66)	10 (62.5)	0.001
	Female	21 (35.59)	5 (29.41)	6 (42.85)	4 (33.33)	6 (37.5)	
Age	≤60	25 (42.37)	8 (47.05)	4 (28.57)	6 (50.0)	7 (43.75)	
	>60	34 (57.62)	9 (52.94)	10 (71.42)	6 (50.0)	9 (56.25)	0.001
Grade	I, II	13 (22.03)	3 (17.64)	3 (21.42)	3 (25.0)	4 (25.0)	
	III, IV	46 (77.96)	14 (82.35)	11 (78.57)	9 (75.0)	12 (75.0)	0.001
Metastasis	Absent	42 (71.18)	6 (35.29)	9 (64.28)	11 (91.66)	16 (100.0)	
	Present	17 (28.81)	11 (64.7)	5 (35.71)	1 (8.33)	0 (0.00)	0.001
P53 mutation	Positive	33 (55.93)	10 (58.82)	7 (50.0)	7 (58.33)	9 (56.25)	0.005
	Negative	26 (44.06)	7 (41.17)	7 (50.0)	5 (41.66)	7 (43.75)	
Ki67	Positive	40 (67.79)	12 (70.58)	10 (71.42)	9 (75.0)	9 (56.25)	0.001
	Negative	19 (32.2)	5 (29.41)	4 (28.57)	3 (25.0)	7 (43.75)	

The results of quantitative Real-Time PCR technique indicated that the expression of SIRT1/Lnc-OC1/GAPDH genes in all grades of disease were significantly higher than normal tissues ($P<0.01$). Also there were significant differences between the expression of SIRT1/Lnc-OC1/GAPDH genes and the grades of cancer ($P<0.05$) (Fig 1, 2).

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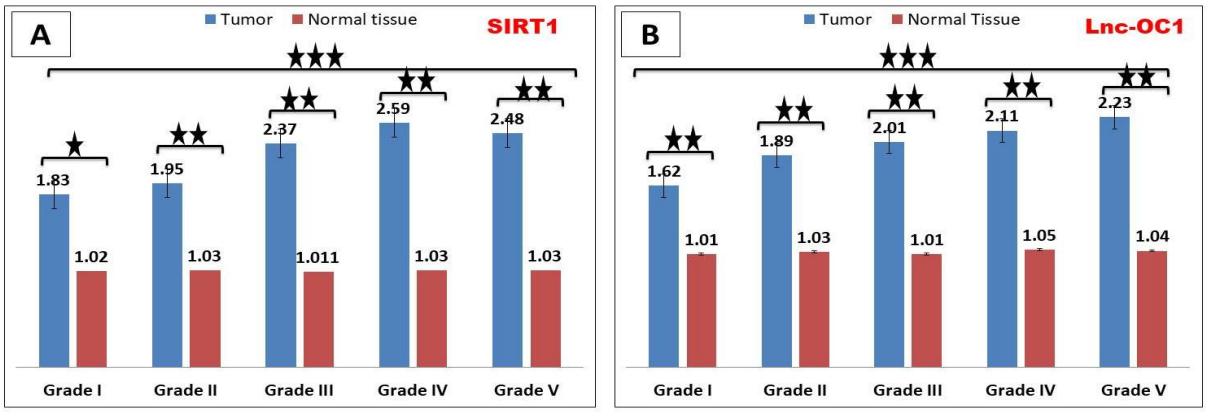

Figure 1. The expression of SIRT1 and Lnc- OC1 genes in different grades of breast cancer in comparison of healthy group. P values were two-tailed, *P < 0.05, **P < 0.01 and***P < 0.001 were considered statistically significant.

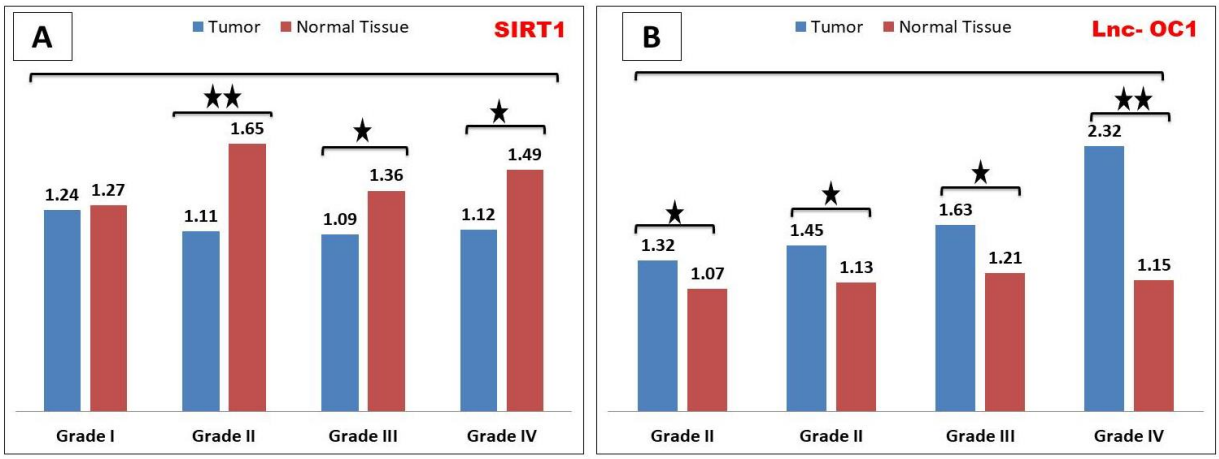

Figure 2. The expression of SIRT1 and Lnc- OC1 genes in different grades of colorectal cancer in comparison of healthy group. P values were two-tailed, *P < 0.05, **P < 0.01 and***P < 0.001 were considered statistically significant.

According to the figure 2, the expressions of SIRT1 gene in all grades were lower than normal tissue. This difference in grade 1 was not significant (P=.0215) but, in grades 2, 3 and 4 were significantly lower (P>0.05). Moreover, no significant differences were observed in different grades (P=0.136). The expressions of lnc-OC1 gene in patients with colorectal cancer in all grades were higher than normal tissue (P>0.05) and the expressions in grade V was significantly higher than other grades (P=0.032).

Discussion

In this study, we examined the expression and SIRT1 and Lnc-OC1 genes in breast and colorectal cancer tissues and corresponding normal tissues using Real-Time PCR technique. The results of current study revealed that the expression of both SIRT1 and Lnc-OC1 genes were increased in patients with breast cancer in comparison to normal tissues. But in colorectal cancer, the expression of SIRT1 gene was decreased whereas the expression of Lnc-OC1 gene

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was increased significantly in comparison to the normal tissues.

Sirtuins are one of the most crucial regulators in neurodegeneration, obesity, age-related disorders, inflammation, heart disease, life-span extension, cancer, other physiological and pathological trials [22]. SIRT1 is the most applicable member in the sirtuin family (SIRT1-SIRT7) that can deacetylate histones and a number of nonhistone substrates such as P53, which have diverse functions in multiple signaling pathways. There are different opinions about the function of SIRT1 and contradictory results have been reported that SIRT1 has both an anti-cancer role and that it strengthens cancer[16]. In different studies, different roles of SIRT1 have been reported. Both the anti-cancer role and the role in cancer progression have been reported.

Yifei et al., (2020) declared that SIRT1 have anti-cancer activity by inhibits the chemoresistance and cancer stemness of gastric cancer by initiating an AMPK/FOXO3 positive feedback loop [23]

On the other hand, Wnt/β-catenin signaling pathway can control the stem cell differentiation, embryo development, as well as tumorigenesis[24]. The results of many previous studies revealed that SIRT1 suppressed the intestinal tumor formation and pancreatic cancer cells by removing the acetylation of β-catenin[25].

In contrast, SIRT1 may have a suppressive activity in tumor cell growth by suppressing the functions of several tumor suppressors' genes such as p53, p73, and HIC1. So it could be suggested that SIRT1 has a sponsoring role in tumor growth and development[26].

In 2017, Sun et al., reported that SIRT1 inhibited the expression of miR-15b-5p by deacetylation of the AP-1 protein as transcription activating factor and increased the levels of acetyl coenzyme A oxidase 1, so leading to reduced migration and invasion of cancer cells [27]. The results of this study are consistent with the results of our study and indicate the suppressive effect of SIRT1 on colorectal cancer.

But in breast cancer, a completely different result has been reported. The results showed that the expression of SIRT1 increased compared to normal tissue. Similarly to current work, in a study conducted by Xiaoxia et al., (2018) reported that overexpression of SIRT1 significantly stimulated breast cancer growth through modulating Akt activity; while down regulation of SIRT1 have anti-cancer effectiveness[28]. In another investigation, Sherine et al., (2016) reported that the level of serum SIRT1 was elevated in patients with Breast cancer among different tumor grades[29].

In the present study, the expression of lnc-OC1 was also reported in patients with colorectal and breast cancers, and in both groups, the expression of this gene in cancerous tissues was significantly higher than normal tissues. The expression of lnc-OC1 gene in 2018 in patients with ovarian cancer was examined and the results indicated that the expression increased significantly in these patients compared to healthy tissue. The results showed that lnc-OC1 as an oncogene is involved in cell proliferation, colony formation, invasion and tumor cell migration. It was also suggested that lnc-OC1 by inhibiting miR-34a/c could be an oncogene and by acting on miR-34 target genes including SIRT1 could play a role in tumorigenesis and cancer progression [30, 31].

Conclusion

In the present study, the expression of SIRT1 and Lnc-OC1 genes in patients with breast and

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colorectal cancer was investigated and the results were compared with the expression of these genes in normal tissues. The expression of SIRT1 in patients with breast cancer increased significantly compared to normal tissues, but decreased in patients with colorectal cancer. In colorectal cancer, it appears that increasing the expression of Lnc-OC1, decreased the expression of SIRT1.

This result, if confirmed by subsequent studies, could be a therapeutic target for patients with colorectal cancer. The expression of Lnc-OC1 gene in patients with breast and colorectal cancer has increased compared to normal tissue, which can be further studied as an indicator of disease prognosis.

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