Original Article

The Expression Patterns of cGAS and STING as Potential Diagnostic Markers in Gastric Cancer

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Abstract

Objective: Gastric cancer (GC) is one of the key causes of cancer-related mortality throughout the world. The cGAS–STING pathway is described as a potential mechanism in cancer immunity and inflammation-mediated tumorigenesis. Accumulating evidence indicate that cGAS–STING pathway is positively related to cancer progression. However, detailed insight into the role of cGAS–STING pathway require further studies. Therefore, understanding the detailed molecular mechanism in the development and progression of GC is of great importance. In the present study, we aimed to evaluate the expression patterns of cGAS and STING and its association with clinicopathological characteristics in gastric cancer patients. **Materials and Methods:** The expression of two candidate genes, including cGAS and STING were evaluated in tumor tissue samples, normal tissue adjacent to the tumor (NAT) biopsies of fifty new case GC patients by PCR method. PBMCs were isolated from forty GC patients and twenty-five non-cancer subjects as the control group. The expression of cGAS and STING in PBMC samples of both GC patients and control group was also evaluated. **Results:** Our results demonstrated a significant increase in cGAS expression along with a non-significant increase in STING expression in tumor samples compared to NAT samples. The expression of cGAS and STING in PBMC samples of GC patients represented a non-significant decrease compared to the control group. **Conclusion:** Our findings could provide detailed insights into the role of the cGAS and STING expression in the progression of GC and contribute to the development of novel therapeutic strategies for GC treatment.

Keywords: cGAS, STING, Gastric Cancer, Innate Immunity, PBMC.

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INTRODUCTION

Gastric cancer (GC) is the fourth leading cause of cancer-related mortality worldwide and has the highest incidence in Asian countries [1,2]. Heterogeneous nature of GC has made it a multifactorial malignancy that both genetic and environmental factors could influence its development [3,4]. Despite recent advances in multidisciplinary approaches to GC treatment including systemic chemotherapy, immunotherapy, surgery, and radiotherapy, prognosis of the disease is poor and the average survival rate is fairly 12 months in the advanced stages [5,6].

Therefore, detailed insights into the molecular mechanisms of GC development are necessary to provide early and accurate detection. Cyclic GMP-AMP synthase (cGAS) is a cytoplasmic sensor for double-stranded DNA (dsDNA), which regulates downstream immune responses in a sequence-independent way [7]. Upon binding to dsDNA, conformational changes in cGAS result in the formation of cyclic GMP-AMP (cGAMP 2'3'), which consequently induce the stimulator of interferon genes (STING) to trigger downstream immune responses [8]. STING is a dimeric adaptor protein located in endoplasmic reticulum (ER) and is known as a key immune adaptor in the diagnosis of cytosolic dsDNA, which is critical for cancer immunity [9,10]. The prominent role of STING in host defense, as well as its pleiotropic effects on cancer cells, are associated with the regulation of type I interferons (IFNs) signaling [11–13]. Binding of STING to cyclic dinucleotides facilitates its interaction with TBK1 cytosolic kinase, which in turn trigger transcription factors such as signal transducer and transcription activator 6 (STAT6) or transcription factor

regulating interferon 3 (IRF3) [14–16]. Nucleus trafficking of STAT6 or IRF3 induces innate immunity mediators such as INF I, NF-κB, and cytokines [17,18].

The cGAS-STING pathway is a key component of sensing cytosolic dsDNA for effective induction of innate immune responses against inflammation and infection [19,20]. Chronic activation of cGAS–STING pathway and downstream immunity mediators is strongly associated with lethal inflammatory disorders [21,22]. In addition, several investigations have indicated onco-suppressive effects of the cGAS-STING pathway as well [23–26]. Cancer cells could prevent activation of the cGAS-STING pathway by intrinsic strategies that enable tumor cells to escape from immune surveillance. These convergent mechanisms include epigenetic modification of cGAS and STING expression, abnormal translational modifications, stimulation of STING degradation, and prohibition of STING signalosome assembly [27]. Suppression of the cGAS-STING pathway in lung cancer cells has been reported to be associated with DNA (Cytosine 5) Methyltransferase 1 binding to cGAS and STING that is induced by increased expression of NEAT1, a tumor intrinsic non-coding RNA [25]. The role of STING in the formation of colorectal tumors in STING-deficient mice models of colitis has been confirmed. Increased levels of colonic pro-inflammatory cytokines were contributed to the excessive proliferation of intestinal epithelial cells in the absence of STING [28]. Increased activity of cGAS-STING pathway in ovarian and colorectal cancer cell lines could induce tumor-infiltrating lymphocytes (TILs) and IFNs [29]. However, the role of cGAS-STING pathway in human GC still remains unclear. In this study, we aimed to evaluate the expression of the cGAS and STING in GC patients and illuminate the role of cGAS-STING pathway in tumor progression and development.

MATERIALS AND METHODS

Ethical approval

Application of tissue samples and all of the methods were performed according to the principles of the amended declaration of Helsinki and were approved by the Research Ethics Committee of Mazandaran University of Medical Sciences (IR.MAZUMS.REC.1398.1295), Sari, Iran, in accordance to the guidelines.

Clinical sample collection

Clinical samples were obtained from patients with gastrointestinal disorders at Imam Khomeini Hospital, Ardabil, Iran after giving written informed consent. Among the candidates for endoscopy, fifty new case patients without immunodeficiency and autoimmune disorders, with no history of chemotherapy and radiotherapy were recruited. Demographic characteristics of patients are depicted in **(Table 1)**. Tumor samples and normal tissue adjacent to the tumor (NAT) of each patient, as well as blood specimens were collected from GC patients. In addition, blood samples of twenty-five healthy subjects at the same age range and gender as GC patients were collected as the control group. No healthy donor had a history of cancer, inflammatory disease, autoimmunity and specific drug consumption.

Table 1. Demographic characteristics of GC patients

Variable		Number	Percent (%)
Age	60<	42	84
	≤ 60	8	16
Gender	Male	35	70
	Female	15	30
Familial history	Yes	9	18
	No	41	82
Tumor location	Cardia	16	32
	Non-Cardia	28	56
	Cardia and Non-Cardia	6	12
Pathology	Diffuse-type	13	26
	Intestinal-type	27	54
	Other	10	20

Preparation of tumor tissue and NAT biopsies

Tumor samples and matched NAT biopsies of the GC patients were provided by the gastroenterologist collected during endoscopy. Samples were immediately transferred to RNA later (Cat. No S-5062, Denazist, Iran) containing microtubes and were stored at -80 ºC.

Isolation of PBMCs

Human PBMCs were isolated from the heparinized peripheral blood sample of both GC patients and control group through density gradient centrifugation utilizing Ficoll with density of 1.077 (Baharafshan-Iran). Briefly, blood samples were diluted with equal volumes of RPMI 1640 medium and was gradually added to the Ficoll in the ratio of 2:1. Samples were centrifuged at 800 g and room temperature for 20 minutes. Cell numbers and viability were determined using the trypan blue dye exclusion method. PBMCs were separated from the middle phase and transferred into 2 ml RNAase-free microtubes and were stored at −80 °C.

RNA extraction and complementary DNA (cDNA) synthesis

Tumor samples and matched NAT biopsies of the GC patients were transferred to sterile RNase-DNase free microtubes containing Trizol One Step RNA Reagent (Cat. No: BS410A, Bio Basic, Canada) and were homogenized (Almagene-Iran) using magnetic beads. RNA from PBMC samples were extracted using Trizol One Step RNA Reagent

(Cat. No: BS410A, Bio Basic, Canada) as well. Extracted RNA samples was electrophoresed on 1% agarose gel and the bands related to 18S and 28S were observed.

Prior to the synthesis of cDNA, the quality of extracted RNA at 260/280 nm and 260/230 nm wavelength ratio was measured by NanoDrop spectrometer (Thermo Scientific™ Nano Drop 2000, USA). Synthesis of cDNA was performed using Yekta Tajhiz cDNA synthesis kit (Yekta Tajhiz, Iran), on T100™ Bio-Rad 96-Well Thermal Cycler.

Quantitative Real-time PCR analysis

The expression of cGAS and STING was evaluated by real-time PCR using specific primers and SYBR Green Real-Time PCR Master Mix (Yekta Tajhiz, Iran). The amplification conditions were as followed: 95 °C for 10 min followed by 40 cycles of 95 °C for 15 s, 58 °C for 30 s, and 72 °C for 25s conducted on Light Cycler 96 Roche (Roche, Germany). All the reactions were caried out in triplicate. The qPCR results were analyzed by the $2^{-\Delta\Delta Ct}$ method. The GAPDH gene was used as a reference gene. The sequences of used primers for the quantification of target genes are listed in (**Table 2)**.

Table 2. List of the primer sequences used for RT-PCR

Genes		**Primer sequence**
STING	Forward	5′GGCATGGTCATATTACATCGG 3′
	Reverse	5′GGGAGGAGAATATACAGCCG3′
cGAS	Forward	5′GGAAGCAACTACGACTAAAGC 3′
	Reverse	5′ATGTGAGAGAAGGATAGCCG 3′
GAPDH	Forward	5′GCTCTCTGCTCCTCCTGTTC3′
	Reverse	5′ACGACCAAATCCGTTGACTC3′

Statistical analysis

Graph Pad Prism statistical software, version 9 (Graph Pad, San Diego, CA, USA) was used for statistical analysis. All data were presented as the mean±standard error (SEM) from triplicate experiments. Student's two-tailed t test was used to evaluate differences between two groups. P value ≤ 0.05 was considered statistically significant.

RESULTS

Expression of cGAS and STING in tumor and NAT samples

The expression of cGAS and STING were evaluated in the context of cancer immunity and development. For this purpose, relative mRNA expression of cGAS and STING were measured in fifty GC tumor samples compared to the expression of both genes in NAT biopsies of each GC case. According to the results, the expression of cGAS was significantly increased ($p<0.05$) while the increase in the STING expression was statistically non-significant ($p\geq0.05$) (**Figure 1**).

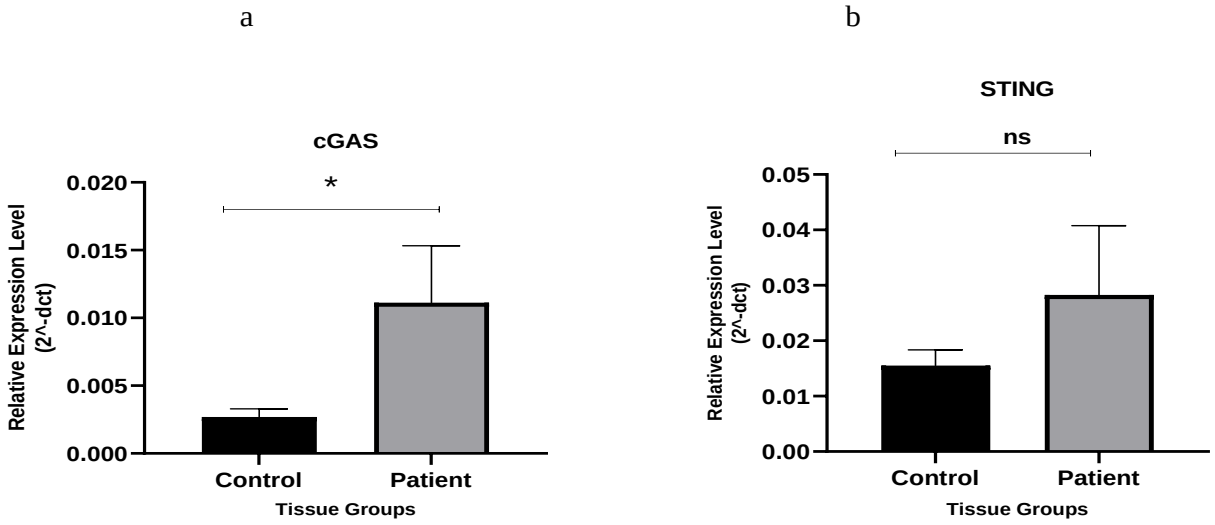
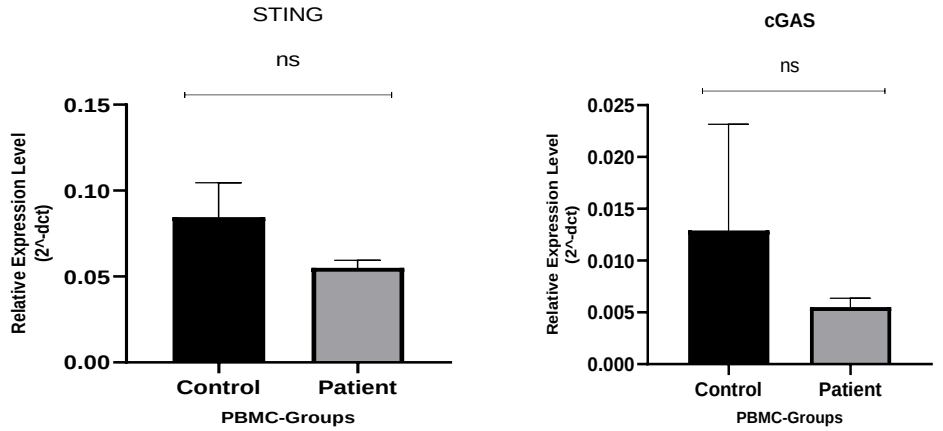


Figure 1. (a) Expression of cGAS in tumor tissue samples and normal tissue adjacent to the tumor (NAT) biopsies of gastric cancer (GC) (P ≤0.05). (b) Expression of STING in tumor tissue samples and normal tissue adjacent to the tumor (NAT) biopsies of gastric cancer (GC). The bars indicate mean±standard error. All experiments were performed in triplicate

Expression of cGAS and STING in PBMC

The relative expression of cGAS and STING mRNAs was further evaluated in PBMC samples in both GC patients and the control group. The results demonstrated a decrease in cGAS and STING expression in the PBMC samples of GC patients in comparison to the healthy subjects (**Figure 2**). However, this decrease was not statistically significant ($p< 0.05$ and $p\geq0.05$ respectively).



a b

Figure 2. (a) Expression of cGAS in PBMC samples of GC patients compared to the control group ($P \geq 0.05$). (b) Expression of STING in PBMC samples of GC patients compared to the control group ($P \geq 0.05$). The bars indicate mean±standard error. All experiments were performed in triplicate.

DISCUSSION

As the first immune barrier of the host, the robust innate immune system has a crucial role in the initiation of adaptive and anti-tumor immunity [8]. The cGAS-STING pathway is a core sensor in the detection of cytosolic dsDNA leading to the activation of innate immunity in response to cancer, inflammation, and infections [30]. Activation of the cGAS-STING pathway is principally associated with sensing both extrinsic and intrinsic self-DNA released from cancer cells [31]. Moreover, mitochondrial DNA scape to the cytosol could activate the cGAS-STING pathway in antiviral immunity. Tan et.al, have revealed the correlation between suppressed cGAS-STING pathway and induced resistance of Head and Neck Squamous Cell Carcinoma (HNSCC) cancer cells to immune mediators [32]. Herein, we investigated the expression of cGAS and STING as key components in the cGAS-STING pathway in the GC patients. The study population consisted of 50 new case GC patients and 25 healthy subjects in the same age range and gender. We evaluated the expression of cGAS and STING in tumor tissue samples compared to their expression in NAT biopsy of each GC case. In addition, the same investigation was performed on the PBMC samples of 40 GC patients compared to the PBMC samples of the control group. 10 GC patients were not allowed for blood sample collection due to the anemia. According to our findings, expression of cGAS and STING in tumor samples of patients were increased compared to the matched NAT biopsies. The increased expression of cGAS was statistically significant ($p \leq 0.05$) while the increase in STING expression was non-significant ($p \geq 0.05$). These findings were in accordance with the study performed by Gammelgaard et.al, [33]. They have evaluated the cGAS-STING pathway in tumor samples and cancer cell lines of non-small cell lung carcinoma (NSCLC). They have reported the increased expression of STING in tumor samples with no significant change in cGAS expression. This could be attributed to the infiltration of immune cells that potentially express STING along with enhanced levels of INF I which in turn leads to the higher expression of STING. Furthermore, they reported a significantly decreased expression of cGAS and STING in the PBMC samples of the patients with cancer compared with patients with localized tumor PBMC samples of the healthy control group. The expression of cGAS in the PBMC samples of the patients was decreased compared with PBMC samples of the non-cancer control group [33].

In our study, we found that the expression of cGAS and STING in the PBMC samples of GC patients was decreased compared to PBMC samples of the control group, but this was not significant ($p\leq 0.05$ and $p\geq0.05$, respectively). The results were in accordance with previously described study.

Loss of expression of the cGAS-STING pathway along with downstream signaling molecules is a key potential in escaping tumor cells from the innate immune system. This

ability of cancer cells has been confirmed by several studies on colorectal cancer and melanoma [34,35]. Although previous research has mainly examined the expression of cGAS-STING pathway in tumor tissue, investigation of this pathway in circulating immune cells is of great importance due to the feasibility of accesses through peripheral blood sample as well as their high expression in PBMCs such as monocytes [36]. Song et.al, have clarified the importance of STING expression in the progression of GC and demonstrated that STING deficiency is positively involved in tumor development due to the loss of DNA sensing potential [37]. The stage-dependent expression of cGAS and STING in tumor tissues has been documented [33]. A study by Yang et al. on the role of cGAS-STING pathway components in the development of colorectal cancer revealed that the expression levels of the cGAS and STING genes were correlated with progression and clinical stages of cancer. Overexpression of cGAS in tumor samples compared to NAT biopsies was associated with the early stages of the disease. They have reported decreased expression of STING in tumor samples of colorectal cancer and the downstream cytokines including IFNB. The results affirmed that loss of DNA sensing in cancer immunity due to reduced expression of STING could positively facilitate tumor surveillance and escape from the immune system [38]. Moreover, reduced expression of STING has been reported to play a critical role in cancer metastasis through immunosurveillance of tumors in later stages of cancer [39]. Correlation of defective STING expression with cancer incidence is identified in several cancers. Inhibited or reduced expression of STING has been documented in melanoma cancer cell lines including SK-MEL-28, SK-MEL-5, G361, WM115, and MeWo [39]. In addition, silenced expression of STING was identified in KRAS-mutated lung cancer, which was associated with decreased expression of LKB1 tumor suppressor gene [40]. Immunohistochemical analysis have further revealed the prognostic role of STING in cancer progression of hepatocellular carcinoma (HCC). Accordingly, decreased expression of STING in HCC tumor samples compared to NAT biopsies was reported to be associated with development of tumor. In addition, advanced tumor node metastasis (TNM) and increased tumor venus infiltration were positively attributed to the reduced expression of STING [41].

Conclusion

Our findings demonstrated that expression of cGAS was significantly upregulated in tumor samples of the GC patients compared to the matched NAT biopsies, as well as a non-significant increase in STING expression. This increase could be associated with the enhanced inflammatory responses in the initial stages of cancer. On the other hand, infiltration of immune cells expressing cGAS and STING is positively correlated with elevated levels of cGAS and STING. Therefore, the increased expression of cGAS and STING in GC patients could be considered as a core sign of GC at early stages. Furthermore, we observed that the expression of cGAS and STING was decreased in the PBMC samples of GC patients in comparison to the control group. The result was referred to the potential of cancer cells to escape sensing by cGAS-STING pathway. However, further studies are required to provide detailed insights into the precise role of cGAS and STING in the development of GC.

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Conflict of Interest

Authors have no conflict of interest.

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