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Research Article

Rs1310191201(C>T) Polymorphism in 3'UTR of *BIRC5*promote Carcinogenesis of Human Gastric Cancer by De-Regulation by Mir-330-5p in Chinese Population

Wenting W[1], Xiaoli T[1], Meixiang Z[2], Chunlei Z[1], and Hu Chengxia[3*]

[1]Department of Clinical Laboratory, The First People's Hospital of Lianyungang, Lianyungang, Jiangsu, China

[2]Department of Clinical Laboratory, 2nd affiliated Hospital of Nanjing Medical University, China

[3]Department of Clinical Laboratory, Suqian Hospital of Traditional Chinese Medicine, Suqian, Jiangsu, China

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***Corresponding author:**

Hu Chengxia, Department of Clinical Laboratory, Suqian Hospital of Traditional Chinese Medicine, Suqian, Jiangsu, China, E-mail: huchengxia119@163.com

1. Abstract

Previous reports have revealed that down-regulation of miR-330-5p expression can promote osteosarcoma growth and invasion by targeting oncogene Baculoviral IAP repeat-containing protein 5 (*BIRC5*). However, the function of the single nucleotide polymorphism (SNP) located in the 3'UTR of *BIRC5* regulated by miR-330-5p has not been investigated in human Gastric Cancer (GC). We found that the rs1310191201 (C>T) polymorphism in the 3'UTR of BIRC5 was involved in the increased occurrence of GC by deregulation effects of BIRC5 miR-330-5p on BIRC5. C>T SNP of 3'UTR of BIRC5 could promote GC cell proliferation by up-regulation of BIRC5. Moreover, C>T SNP of 3'UTR of BIRC5 was statistically related to tumor volume, differentiation and metastasis in GC patients. C>T SNP of 3'UTR of *BIRC5* was related to significantly enhanced expression of *BIRC5* and shorter survival in post-surgery GC patients. Conclusively, rs1310191201(C>T) in 3'UTR of *BIRC5* was highly associated with an increased risk of GC occurrence in a Chinese population and might serve as a novel biomarker for gastric cancer.

2. Abbreviations: GC: Gastric cancer; SNP: Single-nucleotide polymorphism; 3'UTR: Three prime untranslated region; 95% CI: 95 Confidence Interval; HR: Hazard ratio; OD: Odds Ratio; CC: CC genotype in rs1310191201; TT: TT genotype in rs1310191201; C>T: SNP C to T.

3. Keywords: Genotype; MiR-330-5p; Tumor growth; *BIRC5*; SNP

4. Introduction

Gastric cancer (GC) is the sixth most common cancer and the third most common cause of cancer-related death in the world [1]. Although the most frequent correlation for increased gastric cancer risk is not genetic, - it is infection by Helicobacter pylori - genetic predisposition may also play a role [1, 2]. SNPs that have been reported to increase the risk for developing gastric cancer including rs1801133, a SNP in the MTHFR gene [3]. SNPs in the following genes have also been reported to increase gastric cancer risk including PTPN11,TLR4,IL1B - [PMID 17196954], NAT1, TNFA, BMP6, GDF15, RUNX3 etc [3-9]. Besides those SNPs within mature mRNA, SNPs within the 3'UTR a certain gene gain or loss regulation by corresponding miRNA was generally reported recently.

miRNA can decrease the transcription of its target gene by binding to its 3' untranslated region (3' UTR). However, the regulation effect can be affected by many factors; one of the factors is the SNPs within 3'UTR of a certain gene [10, 11]. *BIRC5*, gene symbol for Survivin, is an inhibitor of apoptosis protein (IAP) [12]. Recently, its role has been extensively investigated in gastric cancer [13], however, the reason of various expression of BIRC5 within human GC was not fully explored, and we think the SNPs within its 3'UTR and thus caused deregulation of certain miRNA

&Author contributions: Wenting W, Xiaoli T, Meixiang Z, These authors contributed equally to this work.

is one of the reasons. Therefore, in this study, we focused on the SNPs in the 3'UTR of BIRC5. By using the bioinformatics software, miRNASNP3 (http://bioinfo.life.hust.edu.cn/miRNASNP/#!/), we obtained all the SNPs which could regulate by miRNAs (Table 1). Via the bioinformatics prediction and statistical analysis provided by miRNASNP3, we found that the rs1310191201 (C/T) in *BIRC5* 3'-UTR might potential effect on the regulation by miR-330-5p (Table 2). We further investigated the allele distribution in a case–control study.

Table 1: some of the SNP within 3'UTR of BIRC5.

Gene/ miRNA	SNP ID	Position	Ref/ Alt	Region	Gain	Loss
BIRC5	rs760508738	chr17:78223556	G/T	3'UTR	0	0
BIRC5	rs1188637224	chr17:78223558	C/T	3'UTR	0	0
BIRC5	rs112471026	chr17:78223565	C/T	3'UTR	0	0
BIRC5	rs776613516	chr17:78223566	G/A	3'UTR	0	0
BIRC5	rs1217843298	chr17:78223570	C/G	3'UTR	0	3
BIRC5	rs1170140374	chr17:78223572	G/A	3'UTR	0	9
BIRC5	rs761747371	chr17:78223573	C/G	3'UTR	4	11
BIRC5	rs761747371	chr17:78223573	C/T	3'UTR	1	11
BIRC5	rs370922732	chr17:78223576	G/A	3'UTR	7	10
BIRC5	rs370922732	chr17:78223576	G/T	3'UTR	6	10
BIRC5	rs1310191201	chr17:78223581	C/T	3'UTR	5	17
BIRC5	rs561843820	chr17:78223582	A/G	3'UTR	2	17
BIRC5	rs749926799	chr17:78223591	G/T	3'UTR	4	6
BIRC5	rs1377462147	chr17:78223592	C/G	3'UTR	4	5
BIRC5	rs1396792895	chr17:78223594	C/T	3'UTR	3	6

Table 2: rs1310191201 in *BIRC5* 3'UTR cause miRNAs loss

miRNA	SNP	Gene	miRNA exp.	Gene exp.	Validated by experiment
hsa-miR-1302	rs1310191201	BIRC5	-	531.78	No
hsa-miR-204-3p	rs1310191201	BIRC5	0.81	531.78	No
hsa-miR-3192-5p	rs1310191201	BIRC5	0.09	531.78	No
hsa-miR-326	rs1310191201	BIRC5	8.29	531.78	Yes
hsa-miR-330-5p	rs1310191201	BIRC5	35.83	531.78	Yes
hsa-miR-3649	rs1310191201	BIRC5	-	531.78	No
hsa-miR-3664-5p	rs1310191201	BIRC5	0.27	531.78	No
hsa-miR-4298	rs1310191201	BIRC5	-	531.78	No
hsa-miR-4314	rs1310191201	BIRC5	-	531.78	No
hsa-miR-4646-5p	rs1310191201	BIRC5	0.04	531.78	No
hsa-miR-4714-5p	rs1310191201	BIRC5	0.11	531.78	No
hsa-miR-514a-5p	rs1310191201	BIRC5	4.29	531.78	No
hsa-miR-514a-5p	rs1310191201	BIRC5	4.29	531.78	No
hsa-miR-518c-5p	rs1310191201	BIRC5	27.8	531.78	No
hsa-miR-619-5p	rs1310191201	BIRC5	-	531.78	No

5. Materials and Methods

5.1. Clinical Sample Information

The Hospital-based case-control study consists of 574 patients newly diagnosed with gastric cancer and 574 cancer-free controls. All the subjects were recruited from the 1st people's Hospital of Lianyungang and Suqian Hospital of Chinese traditional medicine, between February 2016 and August 2019. Patients with other hematological disorders, previous history of cancers, radiotherapy and chemotherapy were excluded. The cancer-free control subjects from the same geographic area showed no evidence of a genetic relationship with the cases. The patients were classified according to World Health Organization classification. This study was approved by the Institutional Review Board of the 1st people's Hospital of Lianyungang and and Suqian Hospital of Chinese traditional medicine (LL-16-12 and SCY-17-15), and every patient had written informed consent. The clinical features of all the cases and controls were presented in (Table1).

5.2. Cell Lines and Cell Culture

Gastric cancer cell lines including SGC-7901 and MKN-45 were purchased from American Type Culture Collection. All cells were cultured in Dulbecco modified Eagle medium (DMEM) purchased from Gibco (CA, USA) supplemented with 10 % fetal bovine serum (Invitrogen, Carlsbad, USA) and grown in humidified 5 % CO2 at 37°C.

5.3. Construction of Plasmids

The total cDNA of the *BIRC5* and its 3'UTR, its mutated form were amplified. The PCR production was cloned into the pGL4-promoterless luciferase-based plasmid (Promega, CA, USA). The construction containing miR-330-5p was also synthesized and cloned into p Silence 2.1-U6.

5.4. Dual-Luciferase Reporter Assay

The treated cells harvested 48 h after miRNA treatment, and the firefly luciferase expression was measured and normalized to Renilla activities. Dual-luciferase assays (Promega, Madison, WI) were performed according to the manufacturer's protocol and detected with a Fluoroskan microplate reader (Thermo Labsystems, Helsinki, Finland). Transfection was repeated three times in triplicate.

5.5. Cell Proliferation Assays

Cell proliferation was assayed using CCK-8 (Dojin Laboratories, Kumamoto, Japan) according to the manufacturer's instructions. In short, the control and infected cells were planted at a density of 1×10^4 cells/well in 96-well plates. CCK-8 was added to each well containing 100 μL of the culture medium, and the plate was incubated for 3 h at 37 °C. Viable cells were evaluated by measuring the absorbance at 450 nm, using a microplate reader.

5.6. Immunohistochemistry (IHC)

Sections were stained according to the previous publication. The section was incubated with in primary mouse anti-human Ab for Survivin (ab76424), the sections were stained with DAB according to manufacturer's protocols and mounted and photographed using a digitalized microscope camera (Nikon, Japan).

5.7. Genotyping

Genomic DNA was extracted from peripheral blood by using QIT-Tmp DNA blood mini kits (Qiagen) according to the manufacturer's instructions. Genotyping was performed with the TaqMan SNP Genotyping Assay (4351374, thermo fisher). The PCR reactions were carried out in a total volume of 5 μL containing TaqMan Universal Master Mix, SNP Genotyping Assay Mix, DNase-free water and genomic DNA. The PCR conditions were 2 min at 50°C, 10 min at 95°C, followed by 40 cycles at 95°C for 15 sec and 60°C for 1

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min. The 384-well ABI 7900HT Real-Time PCR System was applied (ABI, thermo fisher, USA).

5.8. Statistical Analysis

All experiments were performed in triplicate and repeated at least three times. Data were expressed as mean ± SD. The association between rs1310191201 genotypes and the risk of GC was evaluated by calculating the odds ratios (ORs) and their 95% confidence intervals (CIs) using univariate and multivariate logistic regression analysis. Differences between two independent groups were tested with Student's t-test. All statistical analyses were carried out using SPSS version 18.0 and presented with Graph pad Prism software. Kaplan–Meier survival curves were plotted, and the log-rank test was done. The significance of various variables for survival was analyzed by the Cox proportional hazards model in a multivariate analysis. The results were statistically significant at $P < 0.05$.

6. Results

6.1. Clinical Significance of Rs1310191201 in GC

We first detected genotype of rs1310191201 in 574 GC cases and 574 healthy controls, the detailed information are listed in (Table 3). As shown in (Table 4), *chi-square* statistical analysis showed that the genotypes of rs1310191201 were followed a Hardy–Weinberg equilibrium distribution pattern in the healthy control group (*P*=0.19) (data not shown). Further statistical analysis demonstrated that the CT genotype and TT genotype presented a significantly increased risk of GC (*P*<0.0001; for CT: Odds Ratio (OR) =1.20, *P*<0.0001 and for TT: OR=2.95, *P*<0.0001). Furthermore, the T carrier group also carried an increased risk of GC (OR=2.08, *P*=0.005). All ORs were adjusted for sex, age, smoking status, drinking history, and family cancer history.

Table 3: Frequency distributions of selected variables in patients and cancer-free controls

Fetures	Cases (*n* = 574)		Controls (*n* = 574)		*P*
	N	*%*			
Age (years)					
≤ 50	324	56.45%	298	51.92%	
> 50	250	43.55%	276	48.08%	
Gender					
Male	276	48.08%	298	51.92%	
Female	298	51.92%	276	48.08%	
Differentiation					
G1-G2	224	39.02%			
G3-G4	350	60.98%			
Tumor Size(cm)					
≤5cm	239	41.64%			
>5cm	335	58.36%			
TMN stage					
I	124	21.60%			
II	165	28.75%			
III	177	30.84%			
IV	108	18.82%			
***H. pylori* infection**					
Positive	348	60.63%			
Negative	226	39.37%			

Table 4: Genotype frequencies of the *BIRC5* rs1310191201 polymorphism among GC cases and controls

Genotype	*Cases* (n =574)		*Controls* (n = 574)		OR	P *Value*a
	N	%	*N*	%	*(95% CI)* a	
rs1310191201						
CC	189	32.93%	274	44.34%	1	
CT	155	27.00%	187	30.26%	1.20 (1.02-1.11)	<**0.0001**
TT	230	40.07%	113	18.28%	2.95 (1.12-1.21)	<**0.0001**
T carrier	385	67.07%	300	48.54%	2.08(1.19-1.29)	**0.005**

6.2. Stratified Analysis of Correlation Between Mir-330-5p Polymorphism and GC

Next, we conducted a stratified analysis to understand the correlation between the SNP *rs1310191201* genotypes and the clinical characteristics of GC patients (Table 5). We found a significant association of thers1310191201 genotypes with the tumor size, poor differentiation, and metastasis. T carrier was related to larger tumor, higher TMN stage and poor differentiation (*P*<0.0001).

Table 5: Stratified analysis of *BIRC5* rs1310191201 genotype with clinicopathological parameters of GC.

Features	CC	CT	TT	T carrier	CC vs. CT	CC vs. TT	CC vs. T carrier
Age (years)							
≤ 50	104	82	138	220	0.7446	0.3214	0.6548
> 50	85	73	92	165			
Gender							
Male	94	84	98	182	0.4483	0.1678	0.5947
Female	95	71	132	203			
Differentiation							
G1-G2	109	56	59	115	<0.0001*	<0.0001*	<0.0001
G3-G4	80	99	171	270			
Tumor Size(cm)							
≤3cm	149	66	24	90	<0.0001*	<0.0001*	<0.0001
>3cm	40	89	206	295			
TMN stage							
I-II	109	84	96	180	0.5852	0.0012*	0.0164
III-IV	80	71	134	205			
H. pylori infection							
Positive	119	79	150	229	0.0285*	0.6823	0.4673
Negative	70	76	80	156			

*Two-sided chi-square test for either genotype distributions or allele frequencies between cases and controls

6.3. The Effect of Rs1310191201 on the Regulatory Role of Mir-330-5p on BIRC5 Expression

Since the SNP rs1310191201 was predicted to be located in the binding site of 3'UTR of BIRC5ofmiR-330-5p, we proposed that the SNP might affect the regulation of BIRC5 by miR-330-5p. We investigated the mimic the SNPs in the 3'UTR of BIRC5 which might cause

de-regulation of miR-330-5p. (Figure 1a). To test whether or not the inhibitory effect by miR-330-5p was impacted by this SNP within the *BIRC5* 3'UTR, we first measured cell proliferation by treated cells transfected with different genotypes of *BIRC5* 3'UTR, including CC and TT. We found that cell proliferation could be suppressed by transfection of miR-330-5p, TT and CC genotypes of *BIRC5* 3'UTR compared to non-3'UTR control, but the proliferation of GC cells transfected by *BIRC5* 3'UTR CC was significantly faster than *BIRC5* 3'UTR TT (Figure 1b). Furthermore, the transcription and expression of Survivin was analyzed by real-time PCR and western-blot which indicated that Survivin expression was significantly decreased in the TT group compared to CC (Figure 1c and d). Next, we constructed pGL4 vectors containing the 3'UTR region of BIRC5 with different genotypes and then co-transfected it with miR-330-5p in GC cell lines. As shown in (Figure 1e), we found that the over-expression of miR-330-5p with the CC genotype could attenuate the suppression caused by miR-330-5p with TT in both gastric cancer cell lines.

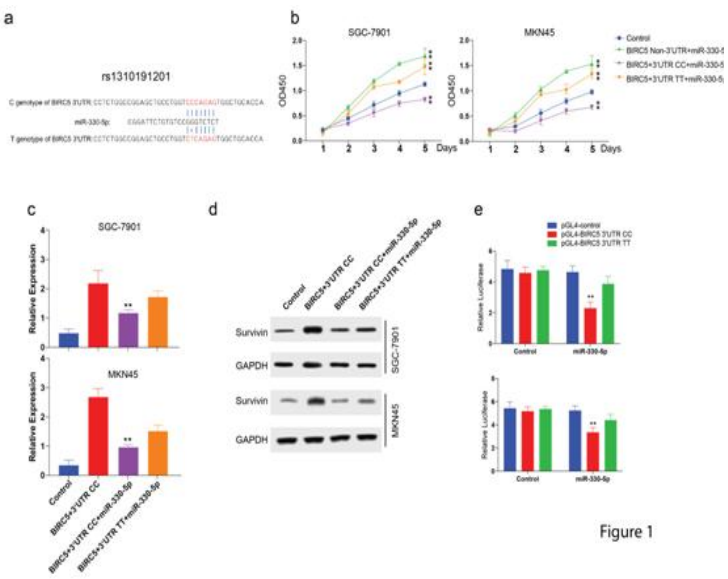

Figure 1: rs1310191201 in 3'UTR of BIRC5on the regulatory of miR-330-5p and cell proliferation.
a Schematic diagram of rs1310191201 in 3'UTR of BIRC5 on the regulatory of miR-330-5p. b Cell proliferation was measured by CCK8 assay in MKN45 and SGC-7901 cell lines. Cells were treated with miR330-5p with or without BIRC5 3'UTR harboring CC or TT genotype and control by vector transfection. c and d Transcription and protein expression of BIRC5 in MKN45 and SGC-7901 treated as indicated in the figure by real-time PCR western blot. e Cells were co-transfected with miR-330-5p with or without BIRC5 3'UTR CC or TT genotype; Renilla luciferase vector pGL3-Luc for 48 h. Both firefly and Renilla luciferase activities were measured in the same sample. Firefly luciferase signals were normalized with Renilla luciferase signals. Data was presented as the mean ± SEM. * indicated P<0.05 and ** indicated P<0.01.

6.4. C/T SNP was Associated with High Expression of BIRC5 and Shorter Post-Operation Survival in Clinical GC Patients

We also measured the expression of BIRC5 in clinical samples with different genotypes of rs1310191201. Survivin expression was detected in human gastric cancer by IHC. The staining was divided into high, medium, and low component categories. The CC group components were significantly different to the T carrier (CT/TT) groups in Survivin expression (strong 24.1%, medium 41.4 %, and low 34.5% for the TT group; strong 25.6%, medium 46.3%, low 28.1% for the CT groups, strong 52.3%, medium 18.3%, and low 29.4% for the CT groups $P<0.001$) (Figure 2a, b). Real-time PCR further confirmed differences in *BIRC5* transcription, but there was no significant difference in miR-330-5p expression between these two groups (Figure 2c, d). All the results above might indicate that the C carrier might serve as a tumor promoter factor in GC by affecting the binding of miR-330-5p on *BIRC5*.

Among the total 570 GC patients, we have 206 patients with follow-up survival data, and these can be further divided into CC (n=89) and T carrier CT/TT (n=117). We assessed the 5-year survival rate in the four groups. The 5-year survival rate in the TT group was 36.2%, which was significantly higher than in the CT/CC group with a survival rate of only 9.35% (95% CI: HR=1.977, P=0.008) (Figure 2E).

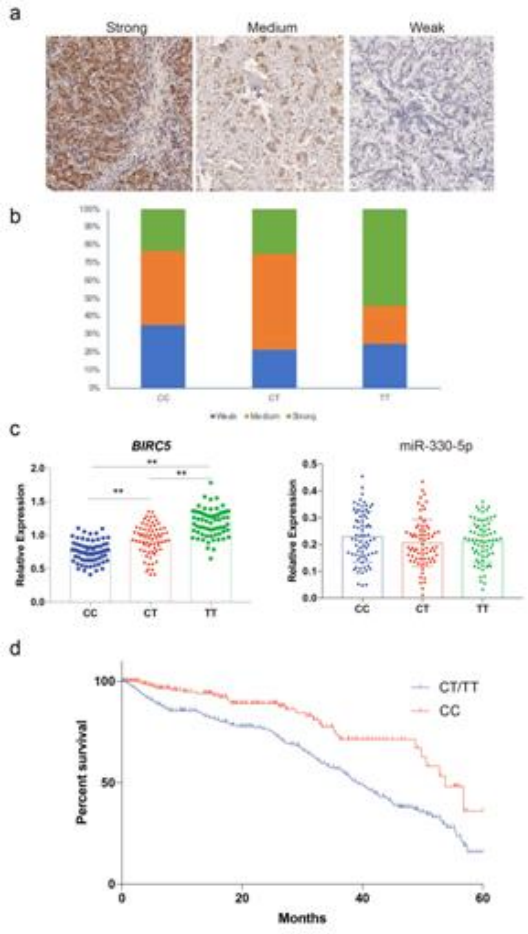

Figure 2: rs1310191201 in miR330-5p on the expression of BIRC5 in clinical samples and overall survival of GC patients
a Representative figures for IHC staining of BIRC5 in GC tumor section. b comparison of component of IHC staining in both in CC, CT and TT genotype GC patients. c and d The expression level of BIRC5 and miR330-5p were determined by Real-time PCR in CC, CT and TT genotype of GC patients. E Overall survival rate of post-surgery GC patients were analyzed by Kaplan-Meier survival curves. Data was presented as the mean ± SEM. * indicated P<0.05 and ** indicated P<0.01.

7. Discussion

BIRC5 expressed in many malignancies including lung, breast, colon, brain, stomach, esophagus, pancreas, liver, prostate cancer etc [14]. In the gastrointestinal tract, there are indications that activation of Survivin may be required for carcinogenesis. Yu et al [15] showed that Survivin expression is frequently (68%) present in gastric cancer tissues and is also present, albeit at lower frequency (27%), in gastric mucosa of first-degree relatives. Survivin expression was also found in 22% of the non-cancerous tissues adjacent to gastric cancer tissues, but was not detectable in almost all the normal, non-adjacent gastric mucosal tissues. Therefore, Survivin barely expressed in normal differentiated tissues, it has become of great interest as both a tumor diagnostic, prognostic marker and as a potential biologic target for future anticancer therapies [14]. The different expression of Survivin within human GC is due to a large of reasons, one of which is miRNA. Although there is no direct evidence shown that miR-330-5p can regulate BIRC5 in human stomach cancer, but such regulations have been reported by different group in human osteosarcoma and myocardiocytes [16, 17]. Our study provided a new insight to explain the expression variance of *BIRC5* in human stomach cancer. The SNP rs1310191201 (C>T) in the 3'UTR of *BIRC5* can cause loss regulation by miR-330-5p, which is a dangerous factor in carcinogenesis of stomach cancer for Chinese population.

miR-330-5p acts as a tumor suppressor in different cancer types. For instance, Kong *et al.* [18] reported that miR-330-5p was significantly decreased in NSCLC, while over expression of miR-330-5p markedly inhibited NSCLC cell growth and promoted cell apoptosis. Lee et al [19] also demonstrated that miR-330 functioned as a tumor suppressor and induced the apoptosis of prostate cancer cells through targeting E2F1. By contrast, miR-330 was found to be upregulated in glioblastoma and to function as an oncogenic factor by enhancing proliferation and invasion, and inhibiting apoptosis through the activation of ERK and phosphoinositide 3-kinase/protein kinase B pathways [20, 21]. Also, more and more study indicated miR-330-5p as a valuable index in gastric cancer diagnosis. Recently, one of the groups reported that circulating miR-330-5p capable of distinguishing patient groups with different diseases of the colon, and moreover, patients with advanced cancer from benign disease groups [19]. In present study, we also confirmed the regulation effect of miR-330-5p on BIRC5 in human gastric cancer, and furthermore, we find its regulation effect can be affected by SNP, C>T genotype in BIRC5 3'UTR was associated with stronger expression of BIRC5 and relatively shorter post-operation survival, this result could be another explanation of variation expression of BIRC5 within human gastric cancer.

8. Conclusions

We report the first evidence that the SNP rs1310191201 located in BIRC5 3'UTR might be a tumor promoter factor by affecting the binding of miR-330-5p, which might further affecting tumor growth in human GC.

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