Original Article

Overexpression of cancer cell-derived immunoglobulin G correlates with poor prognosis in gastric cancer patients

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Background: Various human epithelial origin cancers produce cytoplasmic immunoglobulin (Ig) G. Recent studies have elucidated that it was related with the tumorigenesis. This study was aimed to identify relationship between the cancer cell-derived IgG expression level and clinical parameters in gastric cancer (GC).

Methods: Cancer cell-derived IgG expression was assessed using immunohistochemistry analysis in 231 primary GC tissues. The role of cancer cell-derived IgG on cell proliferation, migration and invasion were assessed.

Results: Our results indicated that IgG was overexpressed in GC tissues (42.2%, 46/109) than in adjacent tissues (11.0%, 12/109, P<0.0001). Positive IgG expression was more frequently detected in patients with TNM III + IV stages when compared with those with TNM I + II stages in GC (48.6% *vs.* 37.2%, respectively). Upon univariate analysis, IgG positive group had significantly lower 5-year overall survival than the negative group (P=0.0361). Multivariate analysis showed IgG expression was an independent prognostic indicator for 5-year overall survival of patients with GC (P=0.018). Furthermore, knockdown of IgG by short interfering RNA (siRNA) resulted in reducing proliferation, migration and invasion of GC cell.

Conclusions: Our results showed that cancer cell-derived IgG overexpression might be correlated with GC progression, and would be a novel biomarker to predict the prognosis of patients with GC.

Keywords: Cancer cell-derived immunoglobulin G; gastric cancer (GC); immunohistochemistry; migration; prognosis

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Introduction

Gastric cancer (GC) is the fourth most prevalent malignant tumor worldwide and the leading cause of cancer-related death in China (1,2). Although the overall prognosis of GC has gradually improved over the past decades, the survival of GC patients is still dismal with the advanced stage or inoperable tumor at the time of diagnosis (3-5). In this context, it is necessary to develop new biomarkers with the potential to estimate the efficacy of therapeutic strategies and prognosis.

Immunoglobulins G (IgG) was first discovered from mature B lymphocytes a century ago and once thought to be unique products of immune cells. Numerous studies introducing structure and biologic function of Ig have been restricted to lymphoid cells (6). However, this traditional view has recently been challenged by Yasuhiko who detected the genes of *IgG* in non-hematopoietic cancer cell lines using the highly sensitive RT-nested PCR method (7). Then, Qiu *et al*. demonstrated IgG protein was produced by cancer cells in both cytoplasmic and secreted forms, and played a potential growth factor role in epithelial origin cancers (8). Cancer cell-expressed immunoglobulin G (CA215) could be used as a monitoring marker for ovarian/cervical cancers (9). In short, recently new evidence displayed Ig could be expressed in proliferating normal cells, epithelial-origin tumor cells and normal mouse central neurons (8,10). The cancer-derived IgG is worlds apart from traditional B-cell derived-IgG in its structure, physicochemical property and biological function. RP215 is a monoclonal antibody specifically recognizing the unidentified glycosylated epitope (CA215C) of heavy chain of cancer-derived IgG (9). Moreover, it has been showed that cancer cell-derived IgG is involved in tumor development and related with lung cancer patient survival (11).

This new concept of cancer cell-derived IgG has been widely accepted. However, the relationship between cancer cell-derived IgG and GC has not been elucidated. In the present study, we analyzed IgG expression (using PR215 antibody) in 231 GC cases by immunohistochemistry and evaluated its correlation with clinicopathological features and prognosis. Our results showed that IgG expression was more frequently detected in patients with TNM III+IV stages and correlated with poor prognosis in patients with GC. Besides, knockdown of IgG by siRNA has impact on the malignant biological behaviors such as proliferation and invasion. These findings suggested that cancer-derived IgG can serve as a prognostic biomarker and therapeutic target in GC.

Methods

Cell culture

GC cell line AGS were purchased from ATCC (Manassas, VA, USA) and BGC-823, MGC-803, MKN28 and SGC-7901 were obtained from the Cell Research Institute (Shanghai, China). All cells were routinely maintained in DMEM medium (GIBCO BRL, Carlsbad, CA, USA), which was supplementing with 10% fetal calf serum (FCS, GIBCO) and penicillin/streptomycin in a humidified atmosphere of 5% CO_2 at 37 ℃.

Two siRNA against IgG (siRNA-1, 5'-GGUGGACAAGACAGUUGAG-3' and siRNA-2, 5'-AGUGCAAGGUCUCCAACAA-3') (12) and non-targeting scrambled siRNA (siControl, 5'-UUCUCCGAACGUGUCAUGUTT-3') were synthesized by GenePharma Corporation (Shanghai, China). Cells (1×105) cultured in 6-well plates for 24 h were transfected with siRNA (100 nmol/L) and Lipofectamine 2,000 reagent (Life Technologies, Carlsbad, CA, USA) in Opti-MEM without serum, according to the manufacturer's instruction.

Patient samples

A total of 231 GC tissues were collected from GC patients who underwent radical gastrectomy at Peking University Beijing Cancer Hospital between January 2002 and December 2007. Among them, 109 patients had gastric cancer and matched adjacent noncancerous tissues. None of the patients received chemotherapy or radiotherapy prior to surgery, and neither had synchronous cancers. All patients signed informed consent forms, and the Ethics Committee of Beijing Cancer Hospital approved tissue collection. Clinicopathological characteristics of patients were obtained from hospital follow-up center. Gastric cancer stage was classified according to the 2010 tumor-node metastasis (TNM) classification recommended by the American Joint Committee on Cancer (AJCC 7th edition). The Overall Survival was calculated by starting from the date of primary tumor operation to the time of death or the last date of follow-up review. In total, 101/231 (43.7%) patients died in the follow-up period.

This study was performed with the approval of the Ethics Committee of Peking of Beijing Cancer Hospital.

Immunohistochemistry (IHC)

All resected tissue specimens were formalin-fixed and paraffin-embedded immediately. Four-micrometer sections were mounted on poly-lysine-coated slides, deparaffinized in xylene, and rehydrated through descending concentrations of ethanol series to ultimately distilled water. Immunohistochemistry analysis was carried out as previously described methods (13). The slides were incubated with RP215 monoclonal antibody (gifted by Prof. XY Qiu, Peking University), which specifically recognized cancer cell-derived IgG (5 μg/mL) overnight at 4 ℃. Immunostaining was detected using two-step diaminobenzidine visualization (Dako, Glostrup, Denmark). Negative controls were carried out with the same procedure in the absence of primary antibody. Histopathological sections were microscopically examined and scored by two independent practiced pathologists who were blind to the patient clinical data. The evaluation was analyzed by no carcinoma cell stained or the percentage of positive cells ≤1% were defined as IgG-negative staining, while the positive stained cells >1% as IgG-positive staining.

Western-blot analysis

Cells were lysed using RIPA buffer (Pierce Biotechnology Rockford, IL, USA) with a protease inhibitor cocktail (Roche, Basel, Switzerland). The Western blotting was performed using standard procedures. The gel-separated proteins were transferred to 0.45 μm polyvinylidene difluoride (PVDF) membrane (Millipore, Billerica, MA, USA) after electrophoresis, then incubated in RP215 (5 μg/mL, gifted by Prof. QX Yan) at 4 ℃ overnight. Goat anti-human Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) antibody (Abcam, Cambridge, MA, USA) was applied as an internal control. Immunoreactive bands were visualized using a chemiluminescence detection system (Pierce, Rockford, USA).

Quantitative RT-PCR

Total RNA was isolated from cancer cells using TRIzol reagent (Life Technologies, Carlsbad, CA, USA), and was reverse transcribed using SuperScript III reverse transcription kit (Life Technologies, Carlsbad, CA, USA). Analysis of mRNA expression was carried out by quantitative PCR using the SYBR green PCR master mix kit (KAPA, Biosystems, USA) with an ABI7500 fast real-time PCR system (Life Technologies, Carlsbad, California, USA) according to the manufacturer's protocol. The primer sequences were designed as follows: IgG (sense) 5'-CAGGACTGGCTGAATGGC-3' and (antisense) 5'-GGCGTGGTCTTGTAGTTGTT-3', and β-actin (sense) 5'-CCTGTGGCATCCACGAAACT-3' and (antisense) 5'-GAAGCATTTGCGGTGGACGAT-3'.

Cell proliferation assays

For cell proliferation assay, cells (4×10^3/well) were plated into 96-well plates in triplicate. Cell viability was assessed using Cell Counting Kit-8 (CCK-8) assay according to the manufacturer's protocol (Dojindo Molecular Technologies, Beijing, China) and quantified at 0, 24, 48, 72 and 96 hours respectively.

Cell migration and invasion assay

Cell migration and invasion assays were performed using Transwell Inserts (Corning Incorporated, USA), which allowed cells to pass through an 8 μm pore size polycarbonate filter with or without Matrigel (Becton Dickinson, San Jose, CA, USA). Equal amounts of cells resuspended in serum-free medium were plated in the upper chamber of each Transwell. The bottom chamber was added with 500 μL complete medium containing 10% FCS. Cells were allowed to migrate for 24 h (migration assay) or 60 h (invasion assay) before cells remained on the upper surface were removed and those penetrated to the undersurface were stained in Cell Stain Solution for 15 minutes. Cell number was counted in four randomly selected microscopic fields (200×) per well.

Statistical analysis

Statistical analyses were carried out using the SPSS software version 19.0 statistical package (SPSS Inc., Chicago, IL, USA). The differences of IgG expression between gastric cancer and adjacent tissues were analyzed by chi-square test. The relationship between IgG expression and patient clinicopathological characteristics were tested with chi-squared test. Survival curves were calculated with the Kaplan-Meier method and the differences in survival assessed by the log-rank test. The effect of different factors on patient survival was performed firstly by univariate Cox proportional hazards model, then by multivariate Cox model for estimating the relative risk of IgG expression.

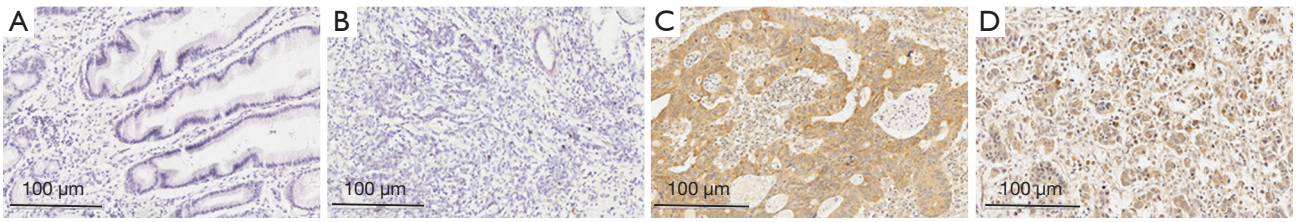

Figure 1 Immunohistochemical staining of cancer cell-derived IgG expression in GC. (A) IgG negative staining in adjacent noncancerous tissues; (B) IgG negative staining in GC; (C) IgG positive staining in intestinal type GC; (D) IgG positive staining in diffuse type GC. Scale bars: A-D =100 μm.

Table 1 Relationship between IgG expression and clinicopathological features of GC patients

Variables	Case No.	IgG expression		P[a] value
		Negative	Positive	
Gender				0.129
Male	169	89	80	
Female	61	39	22	
Age, year				0.100
≤60	55	36	19	
>60	176	93	83	
Differentiation				0.641
Well-moderate	34	19	15	
Poor	113	58	55	
Undetermined	83	51	32	
Lymphovascular invasion				0.556
Absent	116	67	49	
Present	115	62	53	
Depth of invasion				0.153
T1+T2	46	30	16	
T3+T4	185	99	86	
Lymph node metastasis				0.399
No	56	34	22	
Yes	175	95	80	
Distant metastasis				0.262
M0	202	110	92	
M1	29	19	10	
TNM stage				0.095
I+II	86	54	32	
III+IV	140	72	68	

[a], Chi-square test or Fisher's exact test.

The statistical analysis among experimental groups of GC cells was assessed by two-sided Student's *t*-test. P<0.05 were considered as statistical significance.

Results

IgG protein expression in gastric cancer cases

We examined IgG expression in 231 primary GCs (109 samples have cancer and paired adjacent noncancerous tissues) using immunohistochemical analysis. IgG did not express in most of normal gastric mucosa and some of gastric cancer (*Figure 1A*,*B*), but overexpressed in the intestinal and diffuse type in gastric cancer (*Figure 1C*,*D*). The positive staining of IgG predominantly localized in the cytoplasm and cell membrane. IgG was frequently expressed in GC tissues compared with paired adjacent noncancerous mucosa (42.2%, 46/109 *vs*. 11.0%, 12/109, P<0.0001) (*Figure 2A*). Among 231 GC cases, IgG positive cases were 43.7% (101/231).

Association between IgG expression and clinicopathological features in GC

The relationship between IgG expression and clinicopathological features was shown in *Table 1*. The results demonstrated that IgG positive expression more frequently detected in patients with TNM III+IV stages when compared with those in TNM I+II stages in GC (48.6%, 68/140 *vs*. 37.2%, 32/86), although this difference failed to get statistical significance (P=0.095). There was no significant difference between IgG expression and gender, age, lymphovascular invasion, depth of invasion, differentiation, distant metastasis and TNM stage (P>0.05).

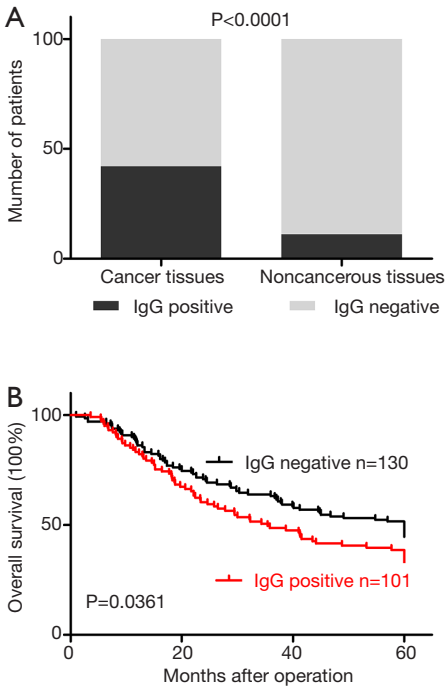

Figure 2 IgG expression in the paired gastric cancer and Kaplan-Meier survival analysis for IgG positive and negative expression. (A) Expression of IgG in Gastric cancer (42.2%, 46/109) and their adjacent noncancerous tissues (11.0%, 12/109); (B) Kaplan-Meier survival curves for 5-year overall survival in GC with IgG positive and negative expression.

IgG expression and survival in patients with GC

Kaplan-Meier survival analysis showed that patients with IgG positive expression had a poorer prognosis than those with negative expression (5-year overall survival rate, 31.6% *vs.* 44.6%, P=0.0361) (*Figure 2B*).

The results of univariate survival analysis for 5-year overall survival of GC patients indicated that lymphovascular invasion, depth of invasion, lymph node metastasis, distant metastasis, TNM stage and IgG expression were significantly affected the survival of GC, respectively (P<0.05). Furthermore, the Cox multivariate model demonstrated that IgG expression level was an independent prognostic factor (P=0.018, HR =1.508, 95% CI: 1.073–2.120). As expected the depth of invasion (P=0.005, HR =2.765, 95% CI: 1.365–5.601), lymph node metastasis (P=0.000, HR =3.564, 95% CI: 1.872–6.787), distant metastasis (P=0.000, HR =5.631, 95% CI: 3.485–9.097) also independently predicted 5-year overall survival (*Table 2*).

IgG promotes proliferative and metastatic ability

We firstly examined the expression of IgG by Western-blot assay in 5 GC cell lines (MKN28, AGS, MGC803, BGC823, and SGC7901) (*Figure 3A*). To investigate the possible role of IgG in GC, the specific siRNAs against IgG were synthesized and transfected to the BGC823 and AGS cells. The efficiency of knockdown was confirmed by RT-PCR (*Figure 3B,C*). As depicted in *Figure 3D,E*, IgG knockdown inhibited cell growth in both BGC823 and AGS cells. The prometastatic capability of IgG was analyzed by migration and invasion assay using transwell chamber. Results showed that cell migration and invasion were significantly reduced in the IgG knockdown cells (P<0.001) (*Figure 4*) compared to siControl. Taking BGC-823 cells as example, cells transfected with siRNA-1 and siRNA-2 showed a 3.3- and 4.8-flod reduction of migration compared to those with siControl, respectively. Likewise, the same tendencies were observed in invasion assay.

Discussion

Gastric cancer is still one of the leading causes of death worldwide. Although it has improved over the past decades for enhancement of cancer awareness, improvement of surveillance systems and multidiscipline treatment, the overall survival rate is still unsatisfactory (1). In this regard, developing sensitive and specific molecular biomarkers is a major challenge in clinical oncology.

Conventional view regards elevated level of Ig in cancer patients as humoral responses of host to cancer cells. However, immunoglobulin genes and proteins have been recently found in different types of cancer cell lines and tissues (10,14-20). This kind of IgG was produced by cancer cells and played vital roles in tumorigenesis. Blockade of tumor-derived IgG increased programmed cell death and inhibited growth of cancer cells *in vitro* (21). Additionally, administration of anti-IgG antibody also suppressed the growth of xenografts in immunodeficient nude mice (8,22). Although the function of traditional IgG in many different cancers has been studied, the expression and effects of cancer cell-derived IgG in GC remains unclear. In the present study, we firstly found cancer cell-derived IgG expression in GC cell lines and primary GC tissues using western-blotting and immunohistochemical analysis, in which RP215 antibody specifically against cancer cell-derived IgG was used (9,23,24).

Previous study indicated that cancer-derived IgG

Table 2 Results of univariate and multivariate Cox's models for OS of GC patients

Variables	Univariate analysis			Multivariate analysis		
	HR	95% CI	P[a] value	HR	95% CI	P[b] value
IgG expression						
Negative *vs*. positive	1.410	1.015–1.961	0.041	1.508	1.073–2.120	0.018
Lymphovascular invasion						
Absent *vs*. present	2.091	1.495–2.925	0.000			
Depth of invasion						
T1+T2 *vs*. T3+T4	5.638	2.866–11.091	0.000	2.765	1.365–5.601	0.005
Lymph node metastasis						
N0 *vs*. N1+2+3	5.856	3.159–10.856	0.000	3.564	1.872–6.787	0.000
Distant metastasis						
M0 *vs*. M1	6.801	4.353–10.627	0.000	5.631	3.485–9.097	0.000
Differentiation						
Well-moderate *vs*. poor	1.097	0.678–1.772	0.707			
Gender						
Male *vs*. female	0.819	0.555–1.210	0.317	0.879	0.590–1.309	0.525
Age						
≤60 *vs*. >60	1.248	0.837–1.859	0.277	1.061	0.700–1.607	0.781

[a], Log-rank test; [b], cox regression test. GC, gastric cancer; HR, hazard ratio.

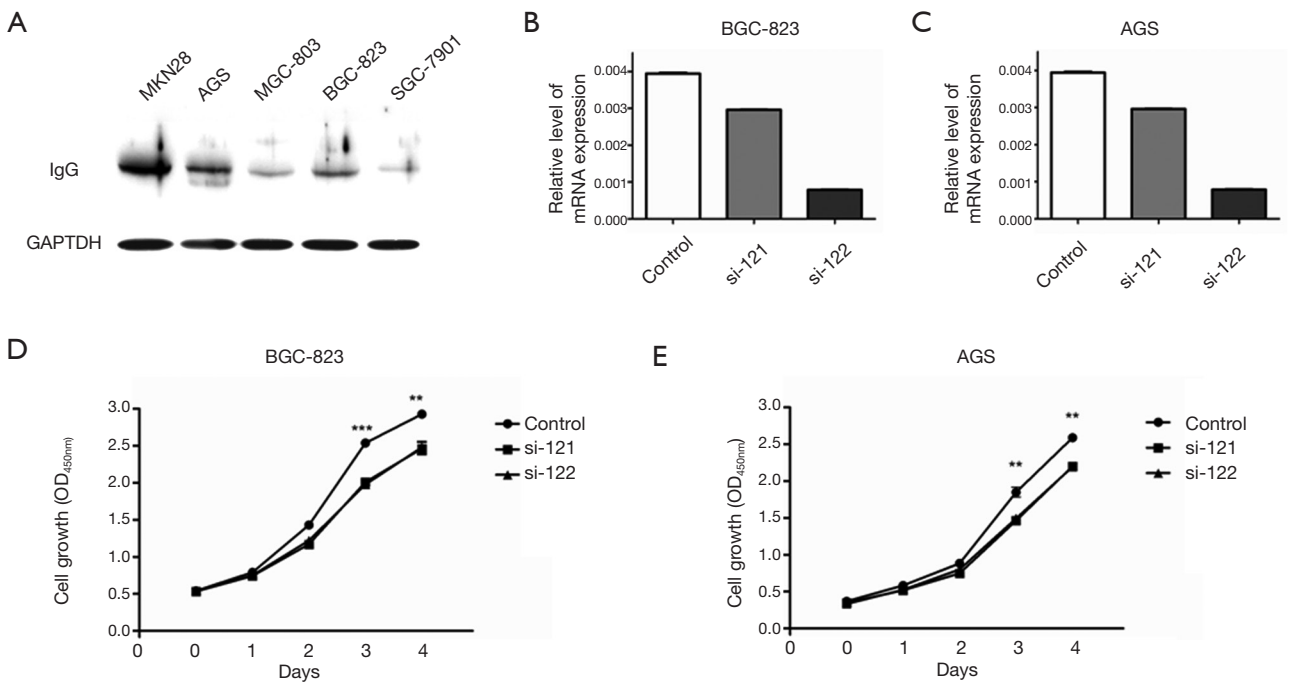

Figure 3 Effects of cancer-derived IgG on cell proliferation. (A) IgG expression level in GC cell lines detected by Western-blot assay; (B,C) efficient IgG silencing was confirmed by RT-PCR; (D,E) growth curves determined by CCK-8 assay in BGC-823 and AGS. All data are shown as mean ± SE of three independent experiments. ** P<0.01; *** P<0.001.

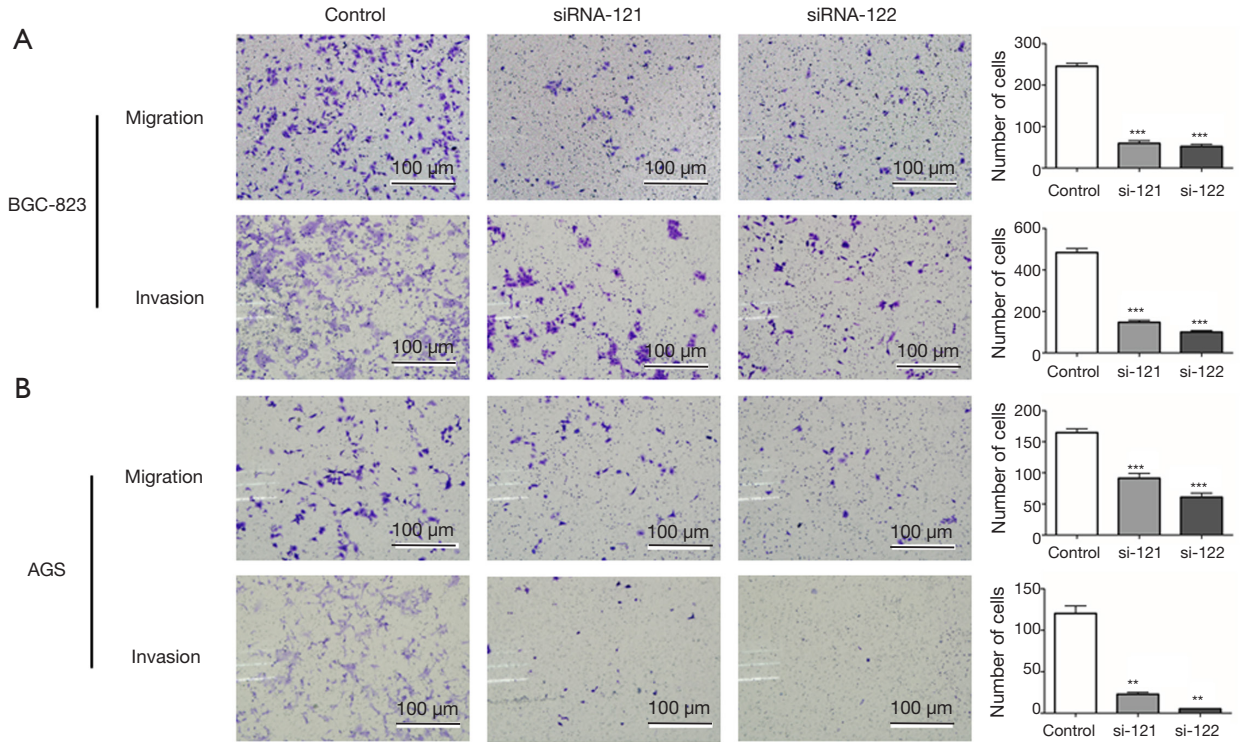

Figure 4 Effects of cancer cell-derived IgG on cell migration and invasion. Migration assay (A and B: left upper panels) and invasion assay (A and B: left lower panels) in BGC-823 and AGS cells transfected with siControl, siRNA-1 and siRNA-2. Quantitative analysis of the number of cells migrated to the lower side of the membrane is shown (A and B: right panel). All data are shown as mean ± SD of three independent experiments. ** P<0.01; *** P<0.001. Scale bars: A, B =100 μm.

overexpression in colorectal cancer was correlated with the expression of Cyclin D1, NF-kB and PCNA, which have been found to be related with more aggressive tumor growth (25). Our present research suggested that IgG was frequently expressed in GC tissues when compared with paired adjacent noncancerous mucosa. High level of IgG expression was more frequently detected in patients with TNM III + IV stages in GC. Multivariate Cox regression analysis showed that IgG expression was an independent prognostic factor in GC patients. The increased expression of IgG in GC tissues and its prognostic indicator showed that cancer cell-derived IgG might present malignant characteristics.

For the function of IgG in GC, we found IgG was involved in biological behaviors by affecting GC cell proliferation, migration and metastasis. Knockdown of IgG using two siRNAs decreased cell proliferation, and suppressed the cell migration and invasion capacity. Thus, it's rational to speculate that, when the tumor ectopically expressed IgG, it might be a promotive signal in tumor progression. These findings were also confirmed by previous studies (12,21,25). Downregulation of IgG in colorectal cancer or lung adenocarcinoma resulted in a reduction of cell migration, invasion and increased cell apoptosis (12,25). Recent study indicated cancer cell-derived IgG exert its cancer progression through MTA1 signaling pathway in lung cancer (26). Wang *et al.* recently reported that cancer cell-derived IgG could affect LPS-induced proinflammatory cytokine production through binding to Toll-like receptors in cervical cancer cells (27). Meanwhile, Wang *et al.* indicated cancer cell-derived IgG can increase cell growth and proliferation via activating MAPK/ERK signaling pathway (28). These investigations suggested that cancer cell-derived IgG might be associated with the malignant potential of tumor cells and would offer a target to cancer therapy and diagnosis.

We have firstly analyzed the expression of cancer cell-derived IgG in GC and its relationship with clinicopathological features. IgG was overexpressed in GC and served as a promising prognostic marker in

management of patients. In addition, IgG played an important role in tumorigenesis and progression by promoting cell proliferation and enhancing cell migration and invasion ability. Our findings suggested IgG could be a candidate target for future gastric cancer diagnosis and therapy.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2016.06.06). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study had been approved by the Research and Ethical Committee of Peking University School of Oncology. A written informed consent had been obtained from each patient participated in this study.

References

1. Hartgrink HH, Jansen EP, van Grieken NC, et al. Gastric cancer. Lancet 2009;374:477-90.
2. Chen WQ, Zheng RS, Zhang SW, et al. The incidences and mortalities of major cancers in China, 2010. Chin J Cancer 2014;33:402-5.
3. Dassen AE, Lemmens VE, van de Poll-Franse LV, et al. Trends in incidence, treatment and survival of gastric adenocarcinoma between 1990 and 2007: a population-based study in the Netherlands. Eur J Cancer 2010;46:1101-10.
4. Macdonald JS, Smalley SR, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med 2001;345:725-30.
5. Cravo M, Fidalgo C, Garrido R, et al. Towards curative therapy in gastric cancer: Faraway, so close! World J Gastroenterol 2015;21:11609-20.
6. Amzel LM, Poljak RJ. Three-dimensional structure of immunoglobulins. Annu Rev Biochem 1979;48:961-97.
7. Kimoto Y. Expression of heavy-chain constant region of immunoglobulin and T-cell receptor gene transcripts in human non-hematopoietic tumor cell lines. Genes Chromosomes Cancer 1998;22:83-6.
8. Qiu X, Zhu X, Zhang L, et al. Human epithelial cancers secrete immunoglobulin g with unidentified specificity to promote growth and survival of tumor cells. Cancer Res 2003;63:6488-95.
9. Lee G. Cancer cell-expressed immunoglobulins: CA215 as a pan cancer marker and its diagnostic applications. Cancer Biomark 2009;5:137-42.
10. Huang J, Zhang L, Ma T, et al. Expression of immunoglobulin gene with classical V-(D)-J rearrangement in mouse testis and epididymis. J Histochem Cytochem 2009;57:339-49.
11. Niu N, Zhang J, Sun Y, et al. Expression and distribution of immunoglobulin G and its receptors in an immune privileged site: the eye. Cell Mol Life Sci 2011;68:2481-92.
12. Liu Y, Liu D, Wang C, et al. Binding of the monoclonal antibody RP215 to immunoglobulin G in metastatic lung adenocarcinomas is correlated with poor prognosis. Histopathology 2015;67:645-53.
13. Shao DF, Wang XH, Li ZY, et al. High-level SAE2 promotes malignant phenotype and predicts outcome in gastric cancer. Am J Cancer Res 2015;5:589-602.
14. Babbage G, Ottensmeier CH, Blaydes J, et al. Immunoglobulin heavy chain locus events and expression of activation-induced cytidine deaminase in epithelial breast cancer cell lines. Cancer Res 2006;66:3996-4000.
15. Zheng H, Li M, Ren W, et al. Expression and secretion of immunoglobulin alpha heavy chain with diverse VDJ recombinations by human epithelial cancer cells. Mol Immunol 2007;44:2221-7.

16. Zhang S, Mao Y, Huang J, et al. Immunoglobulin gene locus events in epithelial cells of lactating mouse mammary glands. Cell Mol Life Sci 2010;67:985-94.
17. Chen Z, Huang X, Ye J, et al. Immunoglobulin G is present in a wide variety of soft tissue tumors and correlates well with proliferation markers and tumor grades. Cancer 2010;116:1953-63.
18. Chen Z, Gu J. Immunoglobulin G expression in carcinomas and cancer cell lines. FASEB J 2007;21:2931-8.
19. Liu Y, Chen Z, Niu N, et al. IgG gene expression and its possible significance in prostate cancers. Prostate 2012;72:690-701.
20. Lei Y, Huang T, Su M, et al. Expression and distribution of immunoglobulin G in the normal liver, hepatocarcinoma and postpartial hepatectomy liver. Lab Invest 2014;94:1283-95.
21. Lee G, Ge B. Inhibition of in vitro tumor cell growth by RP215 monoclonal antibody and antibodies raised against its anti-idiotype antibodies. Cancer Immunol Immunother 2010;59:1347-56.
22. Lee G, Cheung AP, Ge B, et al. CA215 and GnRH receptor as targets for cancer therapy. Cancer Immunol Immunother 2012;61:1805-17.
23. Lee G, Laflamme E, Chien CH, et al. Molecular identity of a pan cancer marker, CA215. Cancer Biol Ther 2008;7:2007-14.
24. Lee G, Cheung AP, Li B, et al. Molecular and immuno-characteristics of immunoglobulin-like glycoproteins in cancer cell-expressed biomarker, CA215. Immunol Invest 2012;41:429-46.
25. Niu N, Zhang J, Huang T, et al. IgG expression in human colorectal cancer and its relationship to cancer cell behaviors. PLoS One 2012;7:e47362.
26. Jiang C, Huang T, Wang Y, et al. Immunoglobulin G expression in lung cancer and its effects on metastasis. PLoS One 2014;9:e97359.
27. Wang J, Lin D, Peng H, et al. Cancer-derived immunoglobulin G promotes LPS-induced proinflammatory cytokine production via binding to TLR4 in cervical cancer cells. Oncotarget 2014;5:9727-43.
28. Wang J, Lin D, Peng H, et al. Cancer-derived immunoglobulin G promotes tumor cell growth and proliferation through inducing production of reactive oxygen species. Cell Death Dis 2013;4:e945.

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