Cancer Medicine

ORIGINAL RESEARCH

CGB5 expression is independently associated with poor overall survival and recurrence-free survival in patients with advanced gastric cancer

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Abstract

The human CGB5 gene encodes chorionic gonadotropin (hCG)β 5, which is aberrantly expressed in trophoblastic neoplasm and in some non-trophoblastic neoplasms. Functional studies observed that it involved tumor initiation, growth, and metastatic outgrowth. In this study, using data from the International Cancer Genome Consortium (ICGC) and the Cancer Genome Atlas (TCGA)-stomach adenocarcinoma (STAD), we assessed the independent prognostic value of CGB5 expression in patients with primary gastric cancer (GC). Results showed that CGB5 expression was nearly not expressed in normal GC tissues. In comparison, its expression was detected in 214 of the 415 primary GC cases (51.6%) in TCGA-STAD and was associated with poor response to primary therapy and a higher risk of recurrence and death. In early stages, CGB5 expression was not a prognostic factor in terms of OS (HR: 1.448; 95% CI: 0.811–2.588, P = 0.211) or RFS (HR: 1.659; 95% CI: 0.778–3.540, P = 0.190). However, its expression was independently associated with unfavorable OS (HR: 1.719; 95% CI: 1.115–2.651, P = 0.014) and RFS (HR: 3.602; 95% CI: 1.708–7.598, P = 0.001) in advanced stages. Using deep sequencing data from TCGA-STAD, we found that CGB5 expression was not related to its genetic amplification or DNA methylation in GC. Based on these findings, we infer that CGB5 expression is common in GC patients and its expression might independently predict poor OS and RFS in advanced stages, but not in early stages of GC.

Introduction

Human chorionic gonadotropin (hCG) is a glycoprotein hormone that plays an important role during pregnancy, such as modulation of implantation, placentation, placental angiogenesis, and maternal/fetal immune responses [1]. As a glycoprotein hormone, hCG is a heterodimers consisting of a common α-subunit and an unique β-subunit which confers biological specificity. Previous studies found that the upregulation of free hCGβ is a marker of the trophoblastic neoplasm, such as choriocarcinoma [2] and its aberrant expression was also observed in some non-trophoblastic neoplasms including endometrial carcinoma and ovarian [3], testicular [4], breast cancer [5, 6], and gastric carcinomas [7].

There are six genes clustered on chromosome 19q13.3 encoding the β-subunit, including CGB1, CGB2, CGB3,
Y. Yang et al., CGB3 into type I gene, while the other three (CGB3, CGB5, and CGB8) were classified into type II genes [9]. A series of previous studies found that dysregulated type II genes are involved in some tumor initiation, growth, and metastatic outgrowth [10], such as colorectal cancer [11] and ovarian cancer [12, 13]. Among the type II genes, the oncogenic mechanisms of aberrantly expressed CGB5 have been characterized in ovarian cancer [12, 13].

hCGβ expression also has a prognostic value in some cancers. In urothelial carcinomas, hCGβ can potentially be used as a marker of patients’ clinical response to treatment [14]. Elevated serum hCGβ and aberrant p53 expression were strongly associated with poor prognosis of serous ovarian carcinoma [3]. One early study based on 54 patients with gastric cancer (GC) found that hCGβ-positive cells can be found in the gastric tumor by immunohistochemical (IHC) staining [15]. However, the expression profile of CGB5 and its prognostic value in GC remains obscure. In this study, using data from the Cancer Genome Atlas (TCGA), we assessed the independent prognostic value of the CGB5 expression in patients with primary GC.

Materials and Methods

Data mining in the International Cancer Genome Consortium (ICGC) and the Cancer Genome Atlas (TCGA)

The ICGC was launched in 2008 to coordinate large-scale cancer genome studies in tumors from 50 cancer types and/or subtypes [16]. In the specimen-centric database, 371 primary GC cases with intact OS data were recorded. The OS data were downloaded using the UCSC Xena browser (https://xenabrowser.net/). In TCGA-Stomach Adenocarcinoma (STAD), 415 GC samples and 35 normal gastric samples were included. Among the 415 patients, 388 cases had intact OS data recorded. The level-3 data, including CGB5 expression (RNAseq - IlluminaHiSeq UNC), age at initial diagnosis, gender, pathological stage, histological grade, radiation therapy, targeted molecular therapy, Helicobacter pylori infection, primary therapy outcome, residual tumor, recurrence status, and living status in this cohort, were also obtained using the UCSC Xena browser. Kaplan–Meier curves of OS and recurrence-free survival (RFS) after primary therapy were generated by GraphPad Prism v6.0 (GraphPad Inc.).

CGB5 Expression and Survivals in Gastric Cancer

CGB5 expression at the protein level in normal human tissues and in cancer tissues was examined using IHC staining data in the Human Protein Atlas (HPA) (http://www.proteinatlas.org/) [17, 18].

Statistical analysis

Gastric cancer patients were divided into CGB5 expression positive (>0) and negative (=0) groups. Statistical analysis was performed using GraphPad Prism v6.0 and SPSS 19.0 (SPSS Inc. Chicago, IL, USA). Continuous variables were reported as means ± standard deviation (SD). The group difference was compared by two-tailed Student’s t-test or ANOVA with Student–Newman–Keuls test as a post hoc test. The association between CGB5 expression and the clinicopathological characteristics was evaluated using χ² tests. Log-rank test was performed to assess the significance of the difference between OS/RFS curves. The prognostic values of CGB5 expression in terms of OS and RFS were analyzed by univariate and multivariate Cox regression models. Linear regression analysis was conducted to assess the correlation between CGB5 expression and its DNA methylation. P < 0.05 was considered statistically significant.

Results

CGB5 expression profiles in GC and normal gastric tissues

By comparing CGB5 expression in TCGA-STAD, we found that CGB5 expression was significantly higher in GC tissues (N = 415) than in normal gastric tissues (N = 35) (Fig. 1A). Among the 415 cases of GC, 214 cases (51.6%) had CGB5 expression (Fig. 1B). By examining CGB5 protein expression in the HPA, we found that CGB5 protein was nearly not detectable in all normal human tissues, except in placenta (Fig. 1C). In normal gastric glandular cells, CGB5 was not detectable by IHC staining (Fig. 1D). In comparison, in 11 cases of GC tissues examined by CGB5 antibody (HPA038934), no positive staining was observed (Fig. 1E, red arrow). However, due to small number of
cases examined, we could not exclude the possibility that some GC tumors might be CGB5 positive.

**Comparison of CGB5 expression in different GC patient groups**

By comparing CGB5 expression between patients with different clinicopathological parameters, we did not find significant difference between female and male patients (Fig. 2A) and among different stages of diseases (Fig. 2B). However, the patients with overall responses to primary therapy [complete remission (CR) and partial remission (PR)] had significantly lower CGB5 expression (Fig. 2C).

Then, we compared the clinical characteristics between the CGB5-positive (>0) and CGB5-negative (=0) groups (Table 1). Results showed that the CGB5-positive group had a lower overall response rate (CR and PR) (110/173, 63.6%) than the CGB5-negative group (137/171, 80.1%) (*P* = 0.0007; Table 1). In addition, we also observed significantly higher ratios of recurrence after primary therapy.
(49/161, 30.4%) and death (93/199, 46.7%) in the CGB5-positive group compared with the negative group (23/163, 14.1%, and 64/189, 33.9%) \((P = 0.0004\) and 0.0098, respectively; Table 1).

**CGB5 expression was independently associated with poor OS in patients with advanced GC**

To explore the association between CGB5 expression and OS in GC patients, we used both data from ICGC and TCGA. By generating Kaplan–Meier curves of OS, we found that CGB5 expression (>0) was associated with shorter OS in primary GC patients, no matter in ICGC \((P = 0.0057)\) (Fig. 3A) or in TCGA-STAD \((P = 0.0014)\) (Fig. 3B). However, in subgroup analysis, we only confirmed the association in advanced stages (stage III/IV) \((P = 0.0017)\) (Fig. 4B), but not in early stages (stage I/II) \((P = 0.21)\) (Fig. 4A). To further investigate the independent prognostic value of CGB5 in terms of OS, univariate and multivariate analysis based on the COX regression model was conducted. In early stages, CGB5
Expression was not a prognostic factor (HR: 1.448; 95% CI: 0.811–2.588, \( P = 0.211 \); Table 2). However, its expression was independently associated with poor OS in advanced stages (HR: 1.719; 95% CI: 1.115–2.651, \( P = 0.014 \); Table 3).

**CGB5 expression was independently associated with poor RFS in patients with advanced GC**

Using RFS as an outcome indicator, we found that CGB5 expression was associated with poor RFS (\( P < 0.0001 \)) (Fig. 5A). Subgroup analysis showed that the association was significant in both early (\( P = 0.028 \)) (Fig. 5B) and advanced stages (\( P = 0.0001 \)) (Fig. 5C). However, CGB5 expression was not an independent prognostic factor of RFS in early stages (HR: 1.659; 95% CI: 0.778–3.540, \( P = 0.190 \); Table 2). In comparison, its expression was independently associated with unfavorable RFS in advanced stages (HR: 3.602; 95% CI: 1.708–7.598, \( P = 0.001 \); Table 3).

**CGB5 expression was not modulated by genetic amplification or DNA methylation in GC**

Then, we tried to explore the mechanisms of CGB5 dysregulation using deep sequencing data from TCGA-STAD. A total of 413 patients had DNA amplification and CGB5 expression measured at the same time (Fig. 6A). No significant difference was observed in different DNA amplification groups (Fig. 6B). A total of 372 patients had CGB5 DNA methylation and RNA expression measured simultaneously (Fig. 6C). Regression analysis showed that there was no significant correlation between CGB5 DNA methylation and its RNA expression (\( P = 0.27 \), Fig. 6D).

**Discussion**

Ectopic expression of hCG\( \beta \) has been associated with malignant behaviors in non-trophoblastic tumors [19]. As CGB5 is one of the key hCG\( \beta \) encoding genes, we examined its expression profile in GC. Interestingly, our data showed that its expression was nearly not expressed in normal GC tissues. In comparison, its expression was detected in 214 of the 415 primary GC cases (51.6%) in TCGA-STAD, suggesting that CGB5 expression was common among the patients. By examining CGB5 protein expression in the HPA, we found that CGB5 protein was not detectable in most of normal human tissues, including normal gastric tissues. Although CGB5 expression was not detected in 11 cases of GC tissues in the database, we could not exclude the possibility that some GC tumors might be CGB5 positive. Besides, we also found that its aberrant expression was significantly related to poor survival.
therapeutic responses. Therefore, in the future, it is meaningful to explore the possible therapeutic value of CGB5-targeting drugs, such as anti-CGB5 or antibody-drug conjugate (ADC) [20, 21], in the potential CGB5-positive cases.

Previous studies found that the structure of hCG\(\beta\) shows significant morphological similarity with that of the "cystine knot growth factor" (CKGF) family members such as transforming growth factor \(\beta\) (TGF\(\beta\)), platelet-derived growth factor B (PDGFB), nerve growth factor (NGF), and vascular endothelial growth factors (VEGFs). The structural similarity suggests that there might be cross talk between these growth regulatory systems [22, 23]. In fact, recent studies demonstrated that hCG acts as a proangiogenic factor in some tumors, which is similar to VEGF [22, 23]. In ovarian cancer, CGB5 could enhance vasculogenic mimicry formation and upregulate the expression of the vascular markers CD31 [12, 24]. In addition, its upregulation also suppresses the apoptosis of the cancer cells by decreasing \textit{B-cell lymphoma 2} (BCL2) and increasing \textit{BCL2-associated X protein} (BAX), and \textit{baculoviral IAP repeat containing 5} (BIRC5) transcription [13]. In addition, HCG\(\beta\) can also modulate the expression of epithelial-mesenchymal transition (EMT)-related genes, including suppressing E-cadherin and increasing phospho-SMAD2, SNAIL and TWIST in colorectal cancer cells, the effects of which are similar to that of TGF\(\beta\) [11]. These findings suggest that hCG\(\beta\) can induce EMT via the TGF\(\beta\) signaling pathway. These mechanisms might help to explain why hCG\(\beta\) upregulation is associated with malignant tumor behaviors.

Currently, clinicopathologic staging is the most important indicator of resectability and prognosis for GC. However, significant variations in response to primary therapies have been observed in patients with the same or similar stages [25, 26]. Therefore, it is meaningful to

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**Table 2. Univariate and multivariate analysis of OS/RFS in stage VII patients in TCGA-STAD.**

| Parameters                        | Univariate analysis | Multivariate analysis |
|-----------------------------------|---------------------|-----------------------|
|                                   | \(P\)  | HR  | 95% CI (lower/upper) | \(P\)  | HR  | 95% CI (lower/upper) |
|-----------------------------------|--------|-----|---------------------|--------|-----|---------------------|
| OS                                |        |     |                     |        |     |                     |
| Age (Continuous)                  | 0.495  | 1.010 | 0.982 | 1.038 | 0.473 | 0.798 | 0.431 | 1.478 |
| Gender                            |        |     |                     |        |     |                     |
| Female vs. Male                   | 0.473  | 0.798 | 0.431 | 1.478 | 0.761 | 0.911 | 0.498 | 1.665 |
| Histological grade                |        |     |                     |        |     |                     |
| G3 vs. G1/G2                      | 0.000  | 3.333 | 1.726 | 6.437 | 0.080 | 1.721 | 0.937 | 3.162 |
| Radiation therapy                 |        |     |                     |        |     |                     |
| No vs. Yes                        | 0.521  | 1.330 | 0.557 | 3.174 | 0.562 | 1.829 | 0.238 | 14.081 |
| Targeted molecular therapy        |        |     |                     |        |     |                     |
| No vs. Yes                        | 0.211  | 1.448 | 0.811 | 2.588 | 0.761 | 0.911 | 0.498 | 1.665 |
| \(H.\) pylori infection           |        |     |                     |        |     |                     |
| No vs. Yes                        | 0.211  | 1.448 | 0.811 | 2.588 | 0.562 | 1.829 | 0.238 | 14.081 |
| Primary therapy outcome           |        |     |                     |        |     |                     |
| SD/PD vs. CR/PR                   | 0.516  | 1.420 | 0.493 | 4.089 | 0.000  | 3.333 | 1.726 | 6.437 |
| CGB5 expression >0 vs. =0         | 0.581  | 0.825 | 0.416 | 1.636 | 0.211  | 1.448 | 0.811 | 2.588 |
| RFS                               |        |     |                     |        |     |                     |
| Age (Continuous)                  | 0.713  | 1.006 | 0.973 | 1.040 | 0.047  | 0.446 | 0.201 | 0.988 |
| Gender                            |        |     |                     |        |     |                     |
| Female vs. Male                   | 0.713  | 1.006 | 0.973 | 1.040 | 0.047  | 0.446 | 0.201 | 0.988 |
| Histological grade                | 0.216  | 0.593 | 0.259 | 1.358 | 0.216  | 0.593 | 0.259 | 1.358 |
| G3 vs. G1/G2                      | 0.174  | 1.631 | 0.806 | 3.299 | 0.216  | 0.593 | 0.259 | 1.358 |
| Radiation therapy                 |        |     |                     |        |     |                     |
| No vs. Yes                        | 0.516  | 1.420 | 0.493 | 4.089 | 0.047  | 0.446 | 0.201 | 0.988 |
| Targeted molecular therapy        |        |     |                     |        |     |                     |
| No vs. Yes                        | 0.211  | 1.448 | 0.811 | 2.588 | 0.047  | 0.446 | 0.201 | 0.988 |
| Primary therapy outcome           | 0.000  | 3.581 | 1.637 | 7.836 | 0.190  | 1.659 | 0.778 | 3.540 |
| SD/PD vs. CR/PR                   |        |     |                     |        |     |                     |
| CGB5 expression >0 vs. =0         |        |     |                     |        |     |                     |

G1, well differentiated (low grade); G2, moderately differentiated (intermediate grade); G3, poorly differentiated (high grade); CR, complete remission; PR, partial remission; SD, stable disease; PD, progressive disease.
| Parameters                                      | Univariate analysis                  | Multivariate analysis                  |
|------------------------------------------------|--------------------------------------|----------------------------------------|
| OS                                             |                                      |                                        |
| Age (Continuous)                               | 0.001 1.035 1.015 1.056              | 0.089 1.019 0.997 1.042                |
| Gender                                         | 0.716 0.925 0.609 1.407              |                                        |
| Female vs. Male                                |                                      |                                        |
| Histological grade                             | 0.210 1.313 0.858 2.009              |                                        |
| G3 vs. G1/G2                                   |                                      |                                        |
| Radiation therapy                              | 0.000 3.663 1.974 6.796              | 0.064 1.954 0.962 3.971                |
| No. vs. Yes                                    |                                      |                                        |
| Targeted Molecular therapy                     | 0.000 2.240 1.472 3.408              | 0.051 1.637 0.999 2.682                |
| No. vs. Yes                                    |                                      |                                        |
| H. pylori infection                            | 0.188 1.868 0.737 4.734              |                                        |
| Primary therapy outcome                        | 0.000 2.811 1.804 4.379              | 0.011 1.858 1.155 2.988                |
| SD/PD vs. CR/PR                                |                                      |                                        |
| Residual tumor                                 | 0.000 2.576 1.577 4.207              | 0.000 2.594 1.528 4.404                |
| R1/R2 vs. R1                                  | 0.000 1.918 1.281 2.870              | 0.014 1.719 1.115 2.651                |
| CGB5 expression >0 vs. =0                     |                                      |                                        |
| RFS                                            |                                      |                                        |
| Age (Continuous)                               | 0.376 0.988 0.961 1.015              |                                        |
| Gender                                         | 0.128 0.543 0.247 1.193              |                                        |
| Female vs. Male                                |                                      |                                        |
| Histological grade                             | 0.088 1.999 0.903 4.426              | 0.049 2.362 1.003 5.565                |
| G3 vs. G1/G2                                   |                                      |                                        |
| Radiation therapy                              | 0.015 3.174 1.257 8.018              | 0.040 2.841 1.048 7.703                |
| No. vs. Yes                                    |                                      |                                        |
| Targeted Molecular therapy                     | 0.467 0.767 0.374 1.570              |                                        |
| No. vs. Yes                                    |                                      |                                        |
| H. pylori infection                            | 0.586 1.522 0.336 6.900              |                                        |
| Primary therapy outcome                        | 0.000 3.686 1.812 7.500              | 0.006 2.810 1.338 5.901                |
| SD/PD vs. CR/PR                                |                                      |                                        |
| Residual tumor                                 | 0.283 1.688 0.650 4.386              |                                        |
| R1/R2 vs. R0                                  | 0.000 3.758 1.830 7.716              | 0.001 3.602 1.708 7.598                |
| CGB5 expression >0 vs. =0                     |                                      |                                        |

G1, well differentiated (low grade); G2, moderately differentiated (intermediate grade); G3, poorly differentiated (high grade); CR, complete remission; PR, partial remission; SD, stable disease; PD, progressive disease; R0, no residual tumor; R1, microscopic residual tumor; R2, macroscopic residual tumor.

**Figure 5.** Kaplan–Meier curves of RFS in GC patients. (A–C) Kaplan–Meier curves of RFS in all patients (A), in early stages group (I/II) (B) and advanced stages group (III/IV) (C). Data were generated using data from TCGA-STAD. Patients were divided into CGB5-positive (>0) and negative (=0) groups.
explore other potential biomarkers of prognosis. Previous studies found that the serum hCGβ level has prognostic values in some cancers. It is an independent prognostic factor in urothelial transitional cell carcinoma (TCC) patients receiving chemotherapy for urothelial TCC in both curative and palliative settings [27]. The OS in hepatocellular carcinoma patients with low serum concentrations of hCGβ is statistically and significantly better than in patients with elevated concentrations [28]. Serum hCGβ level has been shown to be associated with unfavorable prognosis in colorectal cancer [11]. In this study, we also examined the prognostic value of CGB5 in GC using data from two large databases (ICGC and TCGA). Our secondary analysis showed that CGB5 expression was associated with higher ratios of recurrence and death in GC patients. By performing univariate and multivariate analysis based on the COX regression model, we confirmed that CGB5 expression was associated with higher ratios of recurrence and death in GC patients. By performing univariate and multivariate analysis based on the COX regression model, we confirmed that CGB5 expression was associated with higher ratios of recurrence and death in GC patients. Therefore, the exact mechanism of CGB5 expression should be explored in the future. In addition, although we showed the prognostic value of CGB5 expression, more studies are required to characterize the mechanism underlying its expression and GC development and/or therapeutic responses. Elucidation of the CGB5-related signaling pathways is beneficial for future exploration of targeted therapeutic strategies.

**Conclusion**

CGB5 expression is common in GC patients, and its expression might independently predict poor OS and RFS in advanced stages, but not in early stages of GC.

**Conflict of Interest**

The authors have no conflict of interest.

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**Figure 6.** The association between CGB5 expression and its DNA amplification and methylation. (A–B) Heatmap (A) and plots chart (B) of CGB5 expression in groups with different genetic alterations. −1: heterozygous loss, 0: copy-neutral, +1: low-level copy gain, and +2: high-level amplification. Heatmap (C) and regression analysis (D) of the correlation between CGB5 DNA methylation and its RNA expression.
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