Identification of SEC61G as a Novel Prognostic Marker for Predicting Survival and Response to Therapies in Patients with Glioblastoma

Bo Liu, Jingping Liu, Yuxiang Liao, Chen Jin, Zhiping Zhang, Kun Liu, Hao Huang, Hui Cao, Quan Cheng

Background: The survival and therapeutic outcome vary greatly among glioblastoma (GBM) patients. Treatment resistance, including resistance to temozolomide (TMZ) and radiotherapy, is a great obstacle for these therapies. In this study, we aimed to evaluate the predictive value of SEC61G on survival and therapeutic response in GBM patients.

Material/Methods: Survival analyses were performed to assess the correlation between SEC61G expression and survival of GBM patients from the Cancer Genome Atlas (TCGA) and the Chinese Glioma Genome Atlas (CGGA) datasets. Univariate and multivariate Cox proportional hazard regression analysis was introduced to determine prognostic factors with independent impact power. Gene set enrichment analysis (GSEA) and gene set variation analysis (GSVA) were conducted to illustrate possible biological functions of SEC61G.

Results: High expression of SEC61G was significantly correlated with poor prognosis in all GBM patients. High expression of SEC61G was also associated with poor outcome in those who received TMZ treatment or radiotherapy in TCGA GBM cohort. Univariate and multivariate Cox proportional hazards regression analysis demonstrated that SEC61G was an independent prognostic factor affecting the prognosis and therapeutic outcome. The combination of age, SEC61G expression, and MGMT promoter methylation in survival analysis could provide better outcome assessment. Finally, a strong correlation between SEC61G expression and Notch pathway was observed in GSEA and GSVA, which suggested a possible mechanism that SEC61G affected survival and TMZ resistance.

Conclusions: SEC61G expression may be a potential prognostic marker of poor survival, and a predictor of poor outcome to TMZ treatment and radiotherapy in GBM patients.

MeSH Keywords: Drug Resistance • Glioblastoma • Prognosis • Radiotherapy

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Background

Glioblastoma multiforme (GBM) accounts for about 80% of primary malignant brain tumors. The median survival time of GBM is only about 15 months during the past decades [1]. Despite the tremendous progress in post-operative therapies, GBM remains an incurable disease with the highest morbidity. Owing to the unsatisfactory prognosis of GBM, identification of novel prognostic markers or molecular pathways in GBM is urgently needed [2,3].

Postoperative radiotherapy and temozolomide (TMZ) chemotherapy, together with surgery, form the standard treatment for newly diagnosed GBM patients. However, radiotherapy resistance and intrinsic or acquired TMZ resistance represents a major obstacle for these therapies [4–6]. In that sense, it is further important to identify the biomarkers not only related to GBM overall survival, but also related to the outcome of radiotherapy and TMZ chemotherapy [7,8].

SEC61G, also known as Sec61 translocon gamma subunit, is one of the 3 subunits of the Sec61 complex. The Sec61 complex is the central component of the protein translocation apparatus of the endoplasmic reticulum (ER) membrane [9], which is involved in protein folding, modification, translocation, and unfolded protein response especially under conditions of hypoxia and nutrient deprivation in tumor microenvironment [10,11]. SEC61G was found to be overexpressed in gastric cancer [12] and breast carcinomas [13]. SEC61G gene was also investigated to coamplify with epidermal growth factor receptor (EGFR) in 47% of GBMs and overexpressed in 77% of GBMs [14]. However, the correlation between SEC61G and GBM prognosis has not been characterized.

In this study, we comprehensively evaluated the prognostic value of SEC61G expression in GBM patients, especially in those who received TMZ treatment or radiotherapy according to the gene expression profile and corresponding clinical information of GBM patients from the Cancer Genome Atlas (TCGA) and the Chinese Glioma Genome Atlas (CGGA) databases. Bioinformatic methods: gene set enrichment analysis (GSEA) and gene set variation analysis (GSVA) were performed to get further insight into the biological role of SEC61G involved in GBM pathogenesis. We believe our study will contribute to the improvement of molecular diagnosis, prognosis prediction, and individualized therapy for GBM patients.

Material and Methods

Data source

Microarray datasets of 523 GBM patients from TCGA database (http://cancergenome.nih.gov) and 126 GBM patients from the CGGA database (http://www.cgga.org.cn) were obtained to assess the relationship between SEC61G expression and prognosis of GBM patients. Cases lacking gene expression or survival data were excluded. Therapeutic information including TMZ chemotherapy status and radiotherapy status were only available in TCGA microarray dataset. Thus, we used this dataset to evaluate the response to TMZ and radiotherapy in GBM patients. Expression data of SEC61G in different tumors and normal controls were obtained from TCGA and the Genotype-Tissue Expression (GTEX) databases (https://gtexportal.org/home). Expression data of SEC61G in various tumor cell lines were download from the Human Protein Atlas website (http://www.proteinatlas.org).

Gene functional analysis

Gene set enrichment analysis (GSEA) was used to identify the possible gene sets and correlated biological processes or pathways of statistical difference, [NES] >1, P-value <0.05, and FDR q value <0.25 were considered as statistically significant [15]. Additionally, we applied gene set variation analysis (GSVA) to further verify significant differences of biological processes that were defined by gene sets [16]. Ontology gene sets files were obtained from the Gene Ontology (GO) and the Kyoto Encyclopedia of Genes and Genomes (KEGG) databases.

Statistical analysis

All statistical analyses were performed with bioconductor packages in R software (v.3.5.1). Patients with survival time less than 30 days were excluded in survival analyses to avoid potential biases. Kaplan-Meier plots and log-rank test were used to estimate and compare the survival times. The median expression of SEC61G was used to dichotomize patients into either a low-SEC61G or a high-SEC61G group in survival analyses. Univariate and multivariate Cox proportional hazards regression were used to assess the influence of the potential prognostic factors on survival. Pearson correlation analysis was performed to evaluate the association between different genes based on their expression. A P-value <0.05 was regarded as statistically significant in all analyses.

Results

The expression pattern of SEC61G in tumor tissues and tumor cell lines

SEC61G expression was significantly higher in various tumor tissues compared with their normal controls (Figure 1A), which indicated that SEC61G might participate in tumorigenesis in various tumors. High expression of SEC61G was also observed in GBM cell lines, such as U-87MG, U-251MG, and...
SH-SY5Y, which indicated that SEC61G might be a significant marker for GBM (Figure 1B). These results suggested SEC61G as a potential prognostic gene marker.

**Association between SEC61G expression and clinicopathologic factors in GBMs**

We examined SEC61G expression in TCGA and CGGA GBM cohorts stratified by age (<65 years and ≥65 years), molecular type, isocitrate dehydrogenase (IDH) status, and MGMT promoter status. We used 65 years as the cutoff age because the median age of diagnosis of GBM is about 65 years [17]. In TCGA GBM cohort, an increased expression of SEC61G was observed in MGMT promoter methylated, classical, and mesenchymal subtypes, IDH wild-type (WT), and older age (age ≥65 years) groups (Figure 2A). In the CGGA set, an increased expression of SEC61G was observed in classical and mesenchymal subtypes and IDH-WT patients (Figure 2B). There was no significant difference between male and female patients. These findings suggested that GBM patients with high SEC61G expression were prone to have a poorer outcome than those with low expression.

**SEC61G had significant prognostic value in GBM patients**

We used TCGA and CGGA GBM cohorts to investigate the correlation between SEC61G expression and prognosis of GBM patients. Kaplan-Meier plots demonstrated that TCGA GBM patients in the low-SEC61G group had significantly longer overall survival (OS) than those in the high-SEC61G group (P=0.00035). The same trend was also observed in the CGGA GBM cohort (P=0.011, Figure 2C).
Figure 2. The expression pattern of SEC61G in different subgroups and survival analyses of patients with different expression level of SEC61G (median as the cutoff point). (A) SEC61G expression in TCGA GBM cohorts stratified by MGMT promoter status, molecular subtypes, IDH status and ages (<65 years or ≥65 years). (B) SEC61G expression in CGGA GBM cohorts stratified by ages (<65 or ≥65), molecular subtypes and IDH status. * P < 0.05, *** P < 0.001, **** P < 0.0001, ns – not significant. (C) Kaplan-Meier plots of patients in TCGA and CGGA GBM cohorts. (D) Receiver operating characteristic (ROC) curve was plotted to assess the predictive accuracy of SEC61G expression in 3-year survival of GBM patients. TCGA – The Cancer Genome Atlas; GBM – glioblastoma; IDH – isocitrate dehydrogenase; CGGC – Chinese Glioma Genome Atlas.
Receiver operating characteristic (ROC) curves were plotted to assess the predictive accuracy. The area under the curve (AUC) was 0.719 and 0.714 in TCGA and CGGA GBM datasets, respectively (Figure 2D).

Univariate and multivariate Cox proportional hazards regression analyses of relevant clinicopathologic features such as age, gender, molecular types, and MGMT promoter status together with SEC61G expression further confirmed that SEC61G was an independent factor affecting the OS in TCGA GBM cohort (hazards ratio [HR]=1.344, \( P=0.036 \)) (Tables 1, 2). These results indicated that SEC61G might be a predictor for the TMZ response in GBM patients.

SEC61G expression also exhibited stronger predicting power than MGMT promoter status in TCGA GBM patients who received radiotherapy. SEC61G expression showed more significant impact (\( P=0.0014 \)) on survival compared with MGMT promoter status (\( P=0.038 \)) (Figure 3C). In patients without radiotherapy, neither SEC61G nor MGMT promoter status showed significant association with survival, but similarly to the last paragraph, SEC61G expression showed stronger association (\( P=0.13 \)) with survival than MGMT promoter status (\( P=0.46 \)) (Figure 3D). These results indicated that SEC61G might be a predictor for the response to radiotherapy in GBM patients. Additionally, by conducting univariate and multivariate Cox hazards regression analyses of relevant clinicopathologic features such as age, gender and MGMT promoter status together with SEC61G expression, we confirmed SEC61G expression was an independent prognostic factor affecting the response to TMZ (HR=1.436, \( P=0.038 \)) (Figure 3C). In patients without radiotherapy, neither SEC61G nor MGMT promoter status showed significant association with survival, but similarly to the last paragraph, SEC61G expression showed stronger association (\( P=0.13 \)) with survival than MGMT promoter status (\( P=0.46 \)) (Figure 3D). These results indicated that SEC61G might be a predictor for the response to radiotherapy in GBM patients.

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**SEC61G had significant prognostic value in GBM patients who received TMZ treatment or radiotherapy**

We then inspected the correlation between SEC61G expression and survival in TCGA GBM patients who received TMZ treatment to evaluate the response to TMZ treatment. MGMT promoter status was included as a comparison. Kaplan-Meier plots demonstrated SEC61G expression was significantly associated with survival (\( P=0.004 \)), which was more significant than MGMT promoter status (\( P=0.036 \)) (Figure 3A). In GBM patients without TMZ treatment, neither SEC61G expression nor MGMT promoter status showed significant impact on survival, but SEC61G expression showed stronger association (\( P=0.085 \)) with survival than MGMT promoter status (\( P=0.42 \)) (Figure 3B).

**Table 1.** Univariate and multivariate Cox regression analyses of SEC61G expression for GBM patients’ survival in TCGA dataset.

|             | Univariate | Multivariate |
|-------------|------------|--------------|
|             | HR         | 95% CI       | \( P \) value | HR         | 95% CI       | \( P \) value |
| SEC61G (low vs. high) | 1.492 | 1.140–1.952 | 0.004 | 1.344 | 1.008–1.792 | 0.044 |
| Age (<65 vs. ≥65) | 2.195 | 1.641–2.936 | <0.001 | 2.061 | 1.536–2.765 | <0.001 |
| Gender (Male vs. Female) | 0.655 | 0.500–0.858 | 0.002 | 0.614 | 0.466–0.810 | 0.001 |
| Molecular types (CL+ME vs. NE+PN)* | 1.410 | 1.078–1.845 | 0.012 | 1.266 | 0.953–1.681 | 0.103 |
| MGMT (unmethylated vs. methylated) | 0.793 | 0.609–1.032 | 0.085 | 0.855 | 0.655–1.115 | 0.248 |

* CL – classical; ME – mesenchymal; NE – neural; PN – proneural.

**Table 2.** Univariate and multivariate Cox regression analyses of SEC61G expression for GBM patients’ survival in CGGA dataset.

|             | Univariate | Multivariate |
|-------------|------------|--------------|
|             | HR         | 95% CI       | \( P \) value | HR         | 95% CI       | \( P \) value |
| SEC61G (low vs. high) | 1.656 | 1.116–2.456 | 0.012 | 1.598 | 1.031–2.477 | 0.036 |
| Age (<65 vs. ≥65) | 1.350 | 0.494–3.687 | 0.170 | 1.580 | 0.563–4.434 | 0.385 |
| Gender (Male vs. Female) | 0.865 | 0.581–1.286 | 0.473 | 0.895 | 0.597–1.343 | 0.593 |
| Molecular types (CL+ME vs. NE+PN)* | 1.401 | 0.893–2.198 | 0.142 | 1.155 | 0.701–1.901 | 0.572 |

* CL – classical; ME – mesenchymal; NE – neural; PN – proneural.
Figure 3. Comparisons between SEC61G expression and MGMT promoter status in predicting the therapeutic outcomes of TMZ and radiotherapies in TCGA GBM cohort. (A) Kaplan-Meier plots of patients who received TMZ treatment. (B) Kaplan-Meier plots of patients who did not receive TMZ treatment. (C) Kaplan-Meier plots of patients who received radiotherapy. (D) Kaplan-Meier plots of patients who did not receive radiotherapy. TMZ – temozolomide; TCGA – The Cancer Genome Atlas; GBM – glioblastoma.
Prognosis stratification of GBM patients based on age and SEC61G expression

TCGA GBM patients in the age group <65 years had significantly better OS than those in the age group ≥65 years (median survival: 504 days versus 291 days) (P<0.0001). We then added SEC61G expression as a cofactor into the survival analysis in order to obtain more distinct survival prediction. Patients in the age group <65 years with low SEC61G expression had the best OS (median survival: 557 days), which was significantly better than the other age group (Figure 4A). SEC61G expression was significantly correlated with survival among patients age < 65 years, but not among patients age ≥65 years. A possible explanation could be the impact of age on survival was too strong, and it covered up the impact of SEC61G expression in patients older than 65 years. The flowchart of the stratification was shown in Figure 4B. This finding might enable us to estimate the prognosis of GBM patients more accurately.

Prognosis stratification of GBM patients who received TMZ treatment based on MGMT promoter status and SEC61G expression and age

As for GBM patients who received TMZ treatment, patients with methylated MGMT have significantly better OS than those with unmethylated MGMT (median survival: 585 days versus 454 days) (P=0.036). We then added SEC61G expression and age as cofactors into the survival analysis and found that patients with methylated MGMT, low SEC61G expression, and age <65 years had the best OS (median survival: 715 days) (Figure 4C), which was significantly better than the other groups. The flowchart of our stratification is shown in Figure 4D. This finding might enable us to predict the response to TMZ in GBM patients with more accuracy.

SEC61G might be associated with Notch pathway

To illustrate the possible biological functions and pathways of SEC61G in GBMs, we performed GSEA using TCGA and CGGA GBM datasets. Several tumor-related biological processes and pathways, such as macroautophagy, apoptosis, NIK/NF-kappaB signaling, Notch receptor processing, endoplasmic reticulum unfolded protein response, and p53 signaling pathway were significantly enriched in TCGA GBM dataset. While regulation of NIK/NF-kappaB signaling, endoplasmic reticulum unfolded protein response, Notch receptor processing, p53 signaling pathway, JAK-STAT signaling pathway, PI3K-Akt signaling pathway were significantly enriched in CGGA GBM dataset (Figure 5A).

GSVA in TCGA and CGGA GBM datasets generated heatmaps that enrichment score of the related GO terms was depicted along with clinicopathologic factors such as IDH mutation, age, gender, MGMT promoter status, and SEC61G expression level. GSVA further confirmed GO terms such as Notch receptor

| Table 3. Univariate and multivariate Cox regression analyses of SEC61G expression for survival of patients who received TMZ treatment in TCGA dataset. |
|---------------------------------------------------------------|
| **Univariate** | **Multivariate** |
| **HR** | **95% CI** | **P value** | **HR** | **95% CI** | **P value** |
| SEC61G (low vs. high) | 1.409 | 1.017–1.953 | 0.040 | 1.436 | 1.029–2.003 | 0.033 |
| Age (<65 vs. ≥65) | 1.640 | 1.121–2.399 | 0.011 | 1.579 | 1.075–2.317 | 0.020 |
| Gender (Male vs. Female) | 0.654 | 0.469–0.912 | 0.012 | 0.637 | 0.454–0.894 | 0.009 |
| MGMT (unmethylated vs. methylated) | 0.710 | 0.515–0.980 | 0.038 | 0.743 | 0.537–1.028 | 0.077 |

* CL – classical; ME – mesenchymal; NE – neural; PN – proneural.

| Table 4. Univariate and multivariate Cox regression analyses of SEC61G expression for survival of patients who received radiotherapy in TCGA dataset. |
|---------------------------------------------------------------|
| **Univariate** | **Multivariate** |
| **HR** | **95% CI** | **P value** | **HR** | **95% CI** | **P value** |
| SEC61G (low vs. high) | 1.539 | 1.143–2.071 | 0.004 | 1.567 | 1.156–2.123 | 0.004 |
| Age (<65 vs. ≥65) | 1.662 | 1.175–2.352 | 0.004 | 1.566 | 1.102–2.225 | 0.012 |
| Gender (Male vs. Female) | 0.627 | 0.465–0.847 | 0.002 | 0.602 | 0.442–0.819 | 0.001 |
| MGMT (unmethylated vs. methylated) | 0.736 | 0.550–0.985 | 0.039 | 0.803 | 0.598–1.080 | 0.146 |

* CL – classical; ME – mesenchymal; NE – neural; PN – proneural.

Prognosis stratification of GBM patients based on age and SEC61G expression

As for GBM patients who received TMZ treatment, patients with unmethylated MGMT have significant better OS than those with unmethylated MGMT (median survival: 585 days versus 454 days) (P=0.036). We then added SEC61G expression and age as cofactors into the survival analysis and found that patients with methylated MGMT, low SEC61G expression, and age <65 years had the best OS (median survival: 715 days) (Figure 4C), which was significantly better than the other groups. The flow-chart of our stratification is shown in Figure 4D. This finding might enable us to predict the response to TMZ in GBM patients with more accuracy.
processing, regulation of phospholipase A2 activity, and regulation of epithelial to mesenchymal transition were significantly associated with the expression of SEC61G (Figure 5B).

Notch was observed in both GSEA and GSVA. So, we further performed Pearson’s correlation analysis between SEC61G and hub genes of Notch pathway. SEC61G was significantly correlated with Notch hub genes, such as JAG1, PSENEN, and NOTCH4 in TCGA GBM dataset (Figure 5C), and NOTCH3, PSEN2, and NOTCH4 in the CGGA GBM dataset (Figure 5D). These results suggested that the elevated expression of SEC61G might be associated with upregulated Notch pathway in GBMs.

Discussion

This study first investigated a genomic marker related to prognosis and therapeutic response based on different GBM cohorts. We identified SEC61G gene as a potential prognostic marker. High SEC61G expression was significantly correlated to poor outcome of GBM patients. The most impressive finding was that SEC61G expression, even more significantly than MGMT promoter status, could predict the outcome of TMZ treatment. Interestingly, SEC61G also showed significance in predicting the outcome of radiotherapy. We then confirmed SEC61G as an independent impact factor on survival and response to TMZ and radiotherapy. Moreover, as we combined age, MGMT promoter status, and SEC61G expression into the survival analysis, GBM patients with TMZ treatment could be
Therefore, we used MGMT promoter status as a comparison to evaluate the predicting power of SEC61G on TMZ treatment response. In this study, we confirmed MGMT promoter status as a prognostic factor in GBM patients who received TMZ treatment, but not as significant as SEC61G expression, which further confirmed that SEC61G expression was a potential marker for TMZ treatment sensitivity. Beyond that, an unexpected finding was that both MGMT promoter status and SEC61G expression could predict the response to radiotherapy.

As we know, the response to TMZ is not just depend on a single gene signature, but a combination of clinicopathologic features and molecular events [19]. A prognostic assessment model base on multiple factors has become increasingly common, and in this regard, although MGMT promoter methylation is already a well-known biomarker for predicting TMZ treatment response, combining potential prognostic factors such as age and SEC61G expression along with MGMT status could provide further prognostic information for GBM patients than MGMT status alone.

SEC61G encodes a membrane protein, which is 1 of the 3 subunits of the Sec61 complex. The Sec61 complex is the central

**Figure 4.** The combination of multiple factors in survival analyses of TCGA GBM cohort can provide more accurate estimates of outcome. (A) Kaplan-Meier plots of patients in 2 age groups (<65 years versus ≥65 years), and 4 subgroups based on the combination of ages and SEC61G expression. *** P<0.001, MS – median survival. (B) A flowchart to represent the application of our stratification in TCGA GBM cohorts. Patients with age <65 years, low SEC61G expression were found to have significant longer survival than the others (P<0.05). (C) Kaplan-Meier plots of patients who received TMZ treatment, patients were divided into 2 age groups (<65 years versus ≥65 years), and 8 subgroups based on the combination of MGMT promoter status, ages and SEC61G expression. MS represents median survival. (D) A flowchart to represent the application of our stratification in TCGA GBM patients who received TMZ treatment. Patients with age <65 years, low SEC61G expression and methylated MGMT promoter were found to have significant longer survival than the others (P<0.05). TCGA – The Cancer Genome Atlas; GBM – glioblastoma; TMZ – temozolomide.
component of the protein translocation apparatus of the endoplasmic reticulum (ER) membrane [9]. Together with other components such as ERJ1, SEC62, and SEC63, the Sec61 complex is involved in protein folding, modification, and translocation [14]. In addition, the Sec61 complex might also participate in unfolded protein response, which represents a set of cytoprotective activities that enhances anti-apoptosis and the processing capability of misfolded proteins in ER [20,21], especially under conditions of hypoxia and nutrient deprivation in tumor microenvironment [22]. Lu et al. found that SEC61G was over expressed in GBM specimens and cell lines, and that knockdown of SEC61G could inhibit glioma cell proliferation and even result in cell apoptosis. However, their study failed to reveal a correlation between SEC61G and survival of GBM [14]. In our study, significant association between SEC61G expression and GBM prognosis was verified in different GBM cohorts, which

A

GO terms in TCGA dataset

KEGG pathways in TCGA dataset

GO terms in CGGA dataset

KEGG pathways in CGGA dataset

GSVA in TCGA GBM dataset

GSVA in CGGA GBM dataset
at least partly confirmed the results of a previous study that SEC61G exists as a GBM-specific proto-oncogene.

Another important finding was that SEC61G was closely related to the Notch pathway. Notch receptors (Notch 1–4) play an essential role in preventing neuronal differentiation by driving neural stem cell maintenance [23]. As glioma cells share numerous characteristics in common with neural stem cells, Notch is thus often implicated in the development of glioma [24]. Experimental data demonstrated that reduced Notch1 expression in glioma cell lines led to an increased apoptosis and decreased proliferation [25]. On the other hand, Notch was demonstrated to contribute to TMZ resistance in GBM patients; pharmacological antagonism of the Notch pathway could enhance the therapeutic effect of TMZ [26,27]. Notch inhibitors γ-secretase inhibitors (GSIs), could even prolong survival time in GBM patients who received TMZ treatment [28]. Our study demonstrated that SEC61G expression was significantly correlated with the prognosis and TMZ treatment response in GBM patients. So, we speculated these effects of SEC61G might be at least partly caused by the activation of the Notch pathway, which suggested another possible mechanism, that high SEC61G expression could result in a poor prognosis the TMZ resistance in GBM patients.

**Conclusions**

SEC61G is a potential prognostic marker for GBM patients, and an indicator of TMZ and radiotherapy resistance. SEC61G might exert its functions by regulating the Notch pathway in GBM. Further investigations should focus on specific clinical events and biological behaviors associated with SEC61G and the definite mechanism of SEC61G in the regulation network of GBM, which may allow us to better understand the pathogenesis and treatment resistance in GBM patients.

**Conflict of interest**

None.
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