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ORIGINAL RESEARCH

Prognostic significance of EIF4G1 in patients with pancreatic ductal adenocarcinoma

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Background: Advances in genomics have greatly improved the survival rate in cancer patients. However, due to genetic heterogeneity, pancreatic ductal adenocarcinoma (PDAC) is still difficult to diagnose early, and its survival rate is extremely low. Therefore, we identified biomarkers that predict the prognosis of PDAC patients using independent cohort data.

Materials and methods: To develop a novel prognostic biomarker, we used the gene expression and clinical data from The Cancer Genome Atlas (TCGA) and Gene Expression Omnibus (GEO). Kaplan–Meier survival curve using median values of genes as cutoff showed that EIF4G1 was the only statistically significant gene in the 3 cohorts. We analyzed the prognostic significance of EIF4G1 using the time-dependent area under the curve (AUC) of Uno's C-index, the AUC value of the receiver operating characteristics (ROC) at 3 years, and multivariate Cox analysis. We also compared EIF4G1 levels between tumors and matched non-tumor tissues.

Results: EIF4G1 is the only prognostic gene in patients with PDAC, which was selected by Kaplan–Meier survival analysis. The survival curve showed that high expression of EIF4G1 was associated with poor prognosis of PDAC with a good discriminative ability in 3 independent cohorts. The risk stratifying ability of EIF4G1 was demonstrated by analyzing C-indices and AUC values. Multivariate Cox regression confirmed its prognostic significance. EIF4G1 expression was significantly higher in PDAC tissues than in the matched normal tissues.

Conclusion: EIF4G1 could be used as a novel prognostic marker for PDAC and to determine suitable treatment options.

Keywords: EIF4GI, pancreatic ductal adenocarcinoma, prognosis, GEO, TCGA

Introduction

Pancreatic cancer has a very poor prognosis and is difficult to detect early.[1] Of pancreatic cancer cases, 90% are pancreatic ductal adenocarcinoma (PDAC).[2] Only surgical treatment is known to be effective in patients with PDAC. Surgical resection is performed only in 10%–20% of the cases,[3] because most cases are at an advanced stage at the time of diagnosis.[4,5] Moreover, the 5-year survival rate is less than 10% because most patients show relapse or metastasis even if they undergo complete surgical resection.[6] Therefore, biomarkers for PDAC that could predict the prognosis accurately and facilitate early diagnosis are indispensable.

As the importance of precision medicine has been emphasized recently, genomic research is active and its use is expanding from the bench to the bedside, in the actual diagnosis and treatment process.[7,8] Through these efforts, public databases including The Cancer Genome Atlas (TCGA), Gene Expression Omnibus (GEO), and others related to patients with various cancer types and their genomes have been developed, and studies have been actively conducted with these data. Using the data sets in these

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databases and our novel statistical methods, we can report a single gene or set of genes in a specific cancer that can predict prognosis.[9,10]

In the present study, we investigated whether a gene could be used as a biomarker to predict the prognosis of patients with PDAC based on 3 cohorts from TCGA and GEO. Finally, we found the only gene that could predict prognosis in PDAC. Furthermore, the prognosis was found to be stratified according to the gene expression level.

Materials and methods

Patients' data and study design

We investigated all pancreatic cancer cohorts in the GEO database and included only the GSE21501 and GSE28735 data sets in this study, because they contained survival information. The RNA-seq and microarray data and clinical data of PDAC were downloaded from TCGA,[11,12] GSE21501,[13] and GSE28735[14] in March 2018. Patients lacking clinical information were excluded. We identified the prognostic significances of mRNAs in 3 independent cohorts. We then performed paired *t*-test or unpaired (Wilcoxon rank sum test) test to determine whether the statistically significant genes in all cohorts were increased in cancer tissues compared with those in normal tissues using the TCGA or GSE28735 cohorts. The overall process is described in Figure 1. These processes were performed in R software version 3.5.0 (The R Foundation for Statistical Computing, 2018) using the "cgdsr", "TCGAbiolinks", and "GEOquery" R packages.

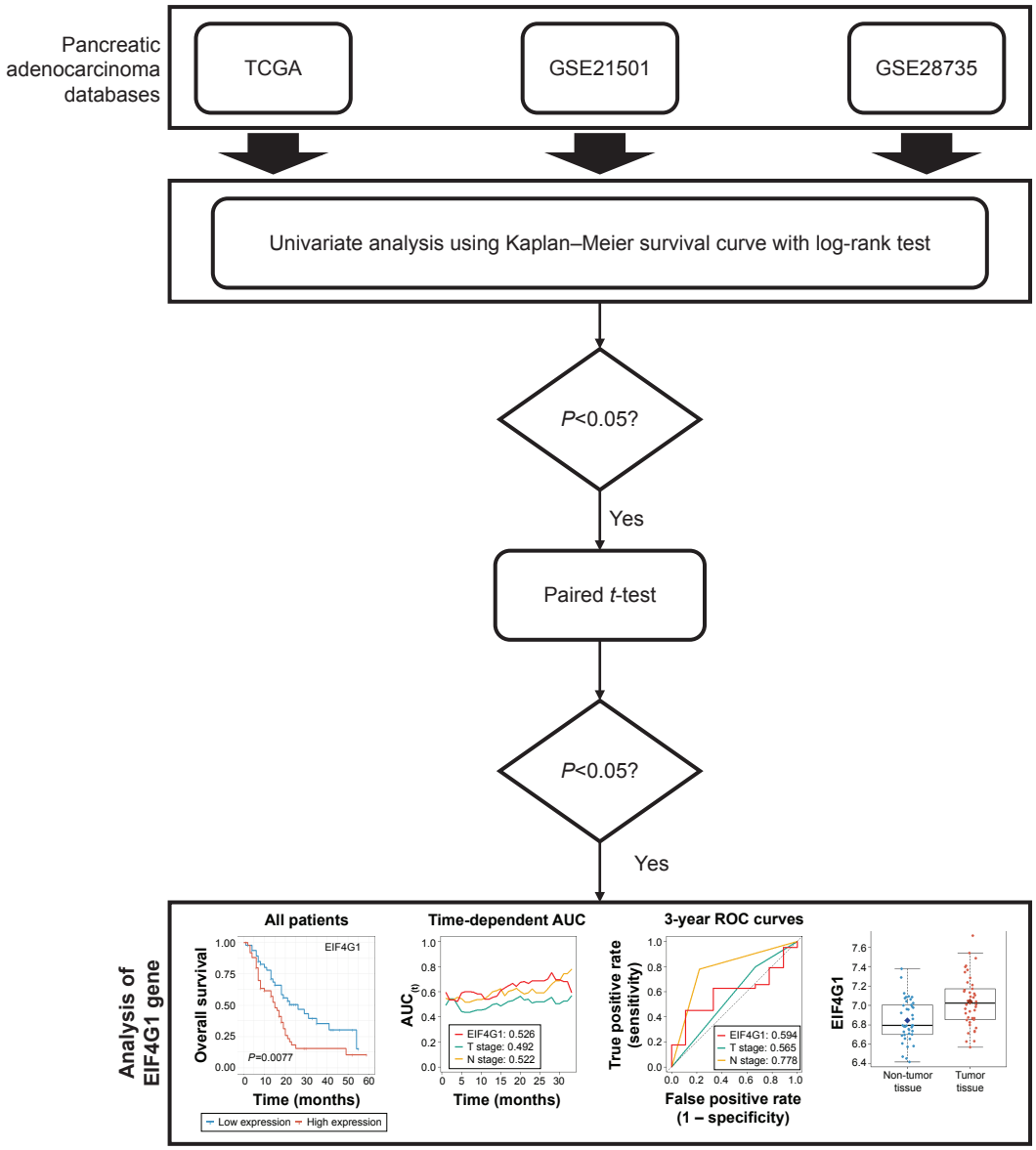

Figure 1 Study protocol.
Abbreviations: AUC, area under the curve; ROC, receiver operating characteristics; TCGA, The Cancer Genome Atlas.

Statistical analysis

Kaplan–Meier survival curves were used to identify the discriminatory power of *EIF4G1*. We determined the optimal cutoff value of the survival curve as described previously.[4,15,16] Furthermore, we used 2 methods to evaluate biomarker performance as follows: 1) Uno's C-index in the time-dependent area under the curve (AUC) analysis and 2) AUC values in receiver operating characteristic (ROC) curves at the 3-year mark as described in our previous studies.[17,18] These values were calculated using the R packages "survival" and "survAUC". The paired *t*-test in the GSE28735 or unpaired test in the TCGA was performed to analyze the *EIF4G1* expression values between the matched tumor and non-tumor tissue samples using the "coin" package. We used uni- and multivariate Cox regression analyses to compare the effect of EIF4G1 on prognosis along with several clinical variables. Additionally, to identify the prognostic significance of miRNAs in TCGA, we used the Oncomir (http://www.oncomir.org), which can analyze survival outcome about miRNAs.[19]

Results

To select the gene that could predict the prognosis of PDAC using public databases, the clinical and genetic information of 316 patients with PDAC from 3 independent cohorts (TCGA, n=172; GSE21501, n=102 and GSE28735, n=42) were downloaded and analyzed. The patient information used in the present study is detailed in Table 1. The patients in TCGA were almost diagnosed at an early stage, whereas the patients in GSE21501 were diagnosed almost at a late stage.

Prognostic performance of *EIF4G1* in PDAC

We obtained the median value of gene expression for all genes in each cohort. Each cohort was divided into 2 groups based on the median value of each gene. The survival of the 2 groups was compared using Kaplan–Meier survival analysis, and statistically significant genes were extracted for each cohort. Among the commonly extracted genes in all 3 cohorts, only *EIF4G1* showed prognostic significance in all 3 cohorts.

We analyzed the Kaplan–Meier curves for survival according to the *EIF4G1* expression level to demonstrate the prognostic performance of *EIF4G1* in PDAC. Intriguingly, lower expression of *EIF4G1* was significantly associated with good prognosis in all 3 cohorts (TCGA, P=0.00053; GSE21501, P=0.0077 and GSE28735, P=0.041) (Figure 2A, D, and G). The results of univariate analysis of overall survival in each cohort suggested that the *EIF4G1* expression level was statistically significant in all cohorts (Table 2). Furthermore, multivariate analysis of the TCGA and GSE21501 demonstrated a significant prognostic performance of *EIF4G1* in PDCA, which was consistent with the abovementioned survival analysis (TCGA, P=0.00132, GSE21501, P=0.025, Table 2). The HR of *EIF4G1* is particularly high when compared to other variables (Table 2). In addition, age in TCGA was a significant variable that could stratify prognosis (P=0.02121, Table 2).

To compare the prognostic significance between miRNAs and *EIF4G1*, we identified the log-rank test results of miRNAs by using Oncomir. There are 216 miRNAs significantly associated with survival in TCGA (Table S1). Unfortunately, because there is no miRNA information in GSE21501 and GSE28735 cohorts, we cannot compare miRNAs and *EIF4G1*.

Biomarker ability of *EIF4G1* in PDAC

We compared Uno's C-index values and AUC values at 3 years for the expression level of *EIF4G1* with other

Table 1 Patients' information used in current research in the TCGA, GSE21501, and GSE28735 cohorts

	Group	TCGA	GSE21501	GSE28735
EIF4G1	All patients	172	102	42
	High expression (event)	58 (40)	54 (39)	24 (16)
	Low expression (event)	114 (52)	48 (27)	18 (13)
Patients' information	Male	94	–	–
	Female	78	–	–
	Stages I and II	164	–	–
	Stages III and IV	8	–	–
	T1 and T2	–	18	–
	T3 and T4	–	80	–
	N0	–	28	–
	N1	–	73	–

Abbreviation: TCGA, The Cancer Genome Atlas.

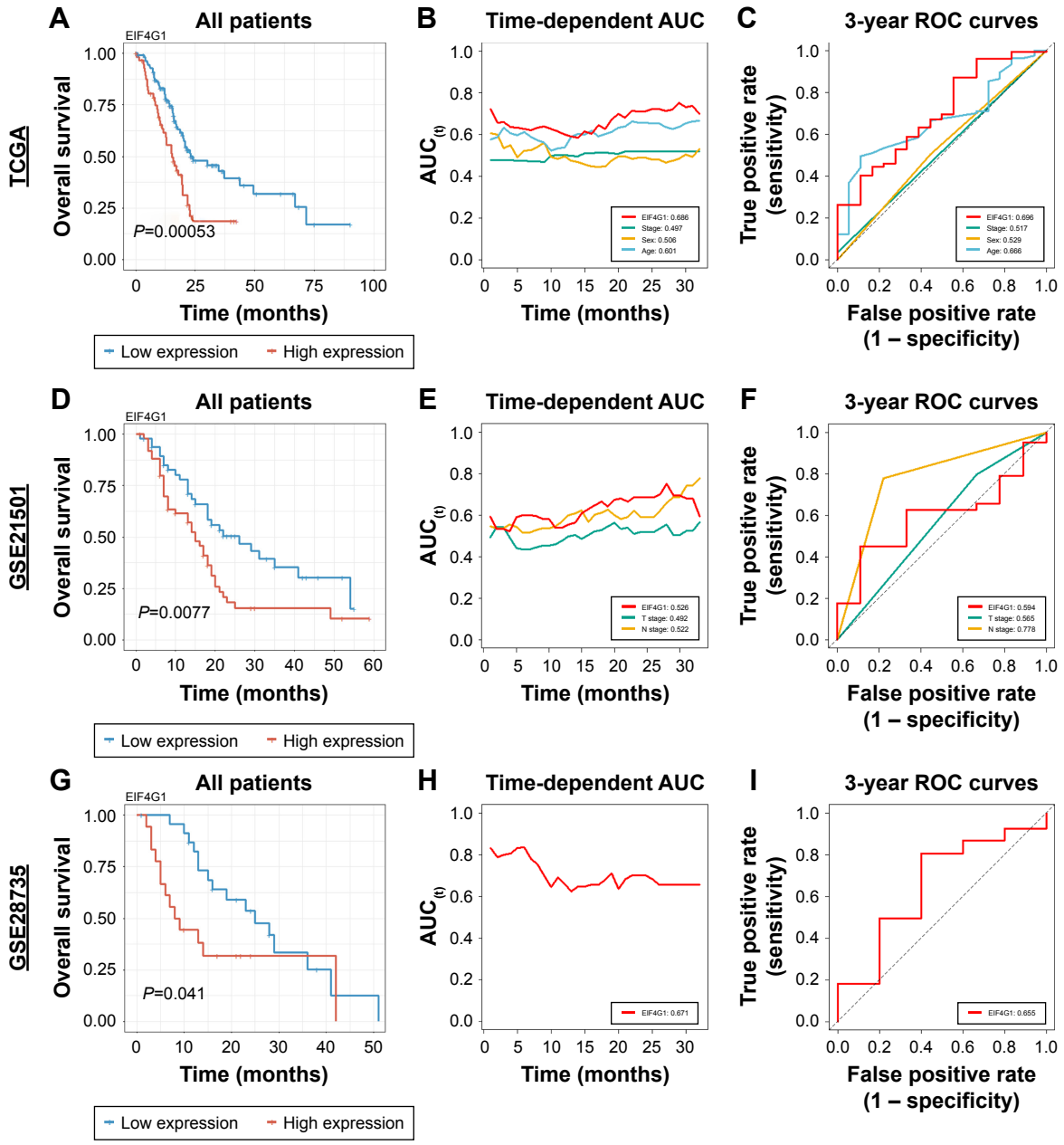

Figure 2 Survival analyses of *EIF4G1* in 3 independent cohorts.

Notes: Kaplan–Meier estimates of all patients in TCGA (**A**), GSE21501 (**D**), and GSE28735 (**G**) according to *EIF4G1* expression. Time-dependent AUC of *EIF4G1* with clinical variables in TCGA (red, EIF4G1; green, stage; yellow, sex; and blue, age) (**B**), GSE21501 (red, EIF4G1; green, T stage; and yellow, N stage) (**E**), and GSE28735 (red, EIF4G1) (**H**). The 3-year ROC of EIF4G1 with clinical variables in TCGA (red, EIF4G1; green, stage; yellow, sex; and blue, age) (**C**), GSE21501 (red, EIF4G1; green, T stage; and yellow, N stage) (**F**), and GSE28735 (red, EIF4G1) (**I**).

Abbreviations: AUC, area under the curve; ROC, receiver operating characteristic; TCGA, The Cancer Genome Atlas.

variables such as tumor staging, sex, and age, which could be obtained from the clinical information of each cohort to examine the ability of *EIF4G1* as a biomarker. *EIF4G1* showed the highest C-index values in 3 independent cohorts (TCGA, 0.686; GSE21501, 0.526; and GSE28735, 0.671; Figure 2B, E, and H). Consistent with the results of Uno's C-index, the 3-year AUC value was slightly less than 0.6 in GSE21501 (0.594; Figure 2F) and nearly 0.7 in the other 2 cohorts (TCGA, 0.696 and GSE28735, 0.655; Figure 2C and I).

Overexpression of *EIF4G1* in PDAC

In order to confirm that *EIF4G1* could predict prognosis as a tumor biomarker, the expression level of EIF4G1 was analyzed in tumor tissues and in non-tumor normal tissues using the GSE28735 or TCGA. Expression level of

Table 2 Univariate and multivariate analyses of overall survival in each cohort

Parameters	Univariate analysis				Multivariate analysis			
	P-value	HR	95% CI		*P*-value	HR	95% CI	
TCGA								
EIF4G1	**<0.0001*** **	**2.072**	**1.359**	**3.157**	**0.00132****	**1.9974**	**1.3093**	**3.047**
Stage	0.716	0.8072	0.2545	2.561	0.7005	0.7968	0.2504	2.535
Sex	0.39	0.8354	0.5543	1.259	0.2903	0.8010	0.5308	1.209
Age	**0.0136***	**1.0261**	**1.005**	**1.047**	**0.02121***	**1.024**	**1.0036**	**1.045**
GSE21501								
EIF4G1	**0.00896****	**1.964**	**1.184**	**3.258**	**0.025***	**1.8076**	**1.077**	**3.034**
T stage (T1 and T2 vs T3 and T4)	0.73	0.8977	0.4862	1.657	0.6047	0.8424	0.4400	1.613
N stage (N0 vs N1)	**0.0425***	**1.8399**	**1.021**	**3.316**	0.0709	1.7773	0.9523	3.317
GSE28735								
EIF4G1	**0.045***	**2.185**	**1.018**	**4.691**				

Notes: Statistically significant values are expressed in bold. *, **, and ***indicate significance at the <0.05, <0.01, and <0.001 respectively.
Abbreviation: TCGA, The Cancer Genome Atlas.

EIF4G1 was significantly higher in the PDAC tissues than in the matched normal tissues in GSE28735 ($P<0.0001$, Figure 3A). In TCGA, *EIF4G1* expression seems to be higher than normal tissues, but it is not statistically significant ($P=0.06196$, Figure 3B).

Discussion

EIF4G1 encodes a scaffold protein upon which ribosomes and the eukaryotic initiation factor (EIF) 4F complex assemble.[20,21] The EIF4F complex regulates the key step of initiation in the translation of almost all genes in eukaryotes.[21,22] Increased E1F4G1 expression has been found in inflammatory breast cancer, lung cancer, hypopharyngeal cancer, and nasopharyngeal cancer, which are consistent with our findings.[20,23] Higher expression of EIF4G1 is also associated with shorter overall survival in various cancers.[20,22–25] EIF4G1 may thus play a tumorigenic role by enhancing the translation of IRES-containing p120 mRNA, which contributes to the survival of breast tumor cells.[22] However, the process by which EIF4G1 has been identified in tumorigenesis has not been fully elucidated in many cancers, including PDAC.

Despite the development of precision medicine, the only prognostic/diagnostic marker for PDAC is CA19-9.[26] Although CA19-9 has been used widely, it is not useful for screening because of its low positive predictive value (<1%). Furthermore, increased false positivity of CA19-9 has been shown in the presence of obstructive jaundice (10%–60%).[27]

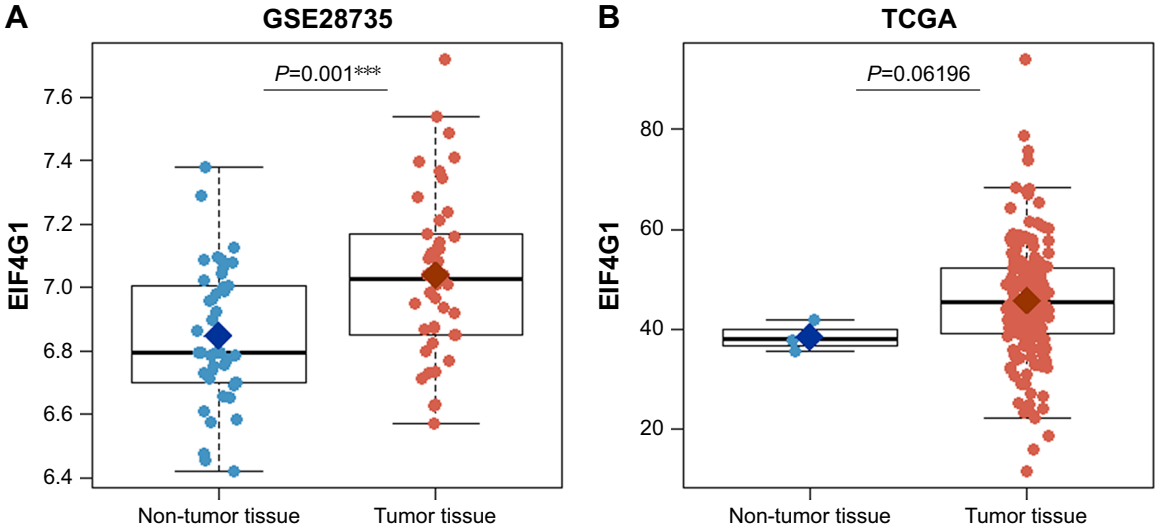

Figure 3 Comparison of EIF4G1 gene expression between matched non-tumor (blue) and tumor tissues (red) in GSE28735 (**A**) or TCGA (**B**).
Note: ***indicates significance at <0.001.
Abbreviation: TCGA, The Cancer Genome Atlas.

Recently, given the importance of molecular markers, many studies have been performed to identify novel biomarkers for pancreatic cancer using multi-omics data.[19,28–30] We also investigated novel prognostic markers in patients with PDAC using 3 independent cohorts from TCGA and GEO databases. As described in Table 1, the patients' information from TCGA and GSE21501 is quite different. *EIF4G1*, which is associated with survival in both cohorts, is likely to be a universal prognostic predictor applied to patients of all stages. Additionally, other clinical variables except for age were not statistically related to survival. These results may be due to the fact that the patient composition of each cohort (TCGA, GSE21501) is biased toward one side.

Conclusion

We demonstrated the prognostic significance of *EIF4G1* in patients with PDAC using public databases. EIF4G1 is known to contribute to tumorigenesis as well as to tumor progression in several cancers. *EIF4G1* is more expressed in cancer tissues and is associated with poor prognosis as its expression increases. We suggest that *EIF4G1* could act as a prognostic biomarker to help determine the precise treatment strategy for PDAC.

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Author contributions

All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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