Molecular and clinical features of a potential immunotherapy target ELK3 in glioma

Hao Xu, MDa, Li Zhang, MDb, Jin Gao, MDc, Jiajing Wang, MDd, Yihao Wang, MDd, Dongdong Xiao, MDd, Songshan Chai, MDc,*

Abstract
Glioma represents the most prevalent malignant primary brain cancer, and its treatment remains a tremendous challenge. Novel and efficient molecular targets are therefore required for improving diagnosis, survival prediction, and treatment outcomes. Additionally, some studies have shown that immunity is highly associated with glioma progression. Our study aimed to investigate the clinicopathological features, prognostic significance, and immunotherapeutic targetability of ELK3, a member of the erythroblast transformation-specific transcription factor family, in glioma using bioinformatics analyses. ELK3 transcript levels in glioma tissues were evaluated using the Gene Expression Omnibus and The Cancer Genome Atlas databases. Clinical and transcriptomic data of The Cancer Genome Atlas glioma patients were analyzed to identify the molecular and clinical characterizations of ELK3. The prognostic significance of ELK3 was assessed using Cox regression and Kaplan–Meier analysis. The biological pathways related to ELK3 expression were identified by gene set enrichment analysis. The relationships between ELK3 and inflammatory responses, immune cell infiltration, and immune checkpoints were explored using canonical correlation analysis and gene set variation analysis. ELK3 was upregulated in gliomas, and its high expression was correlated with advanced clinicopathologic features and unfavorable prognosis. Gene set enrichment analysis revealed that several immune-related pathways were tightly linked to high ELK3 expression. Gene set variation analysis and correlograms demonstrated that ELK3 was robustly associated with inflammatory and immune responses. Correlation analyses indicated that ELK3 was positively associated with infiltrating immune cells and synergistic with several immune checkpoints. ELK3 may serve as a novel marker of poor prognosis and a potential immunotherapeutic target in glioma.

Abbreviations: B7-H3 = designated B7 homolog 3, B7-H4 = designated B7 homolog 4, CTLA-4 = cytotoxic T-lymphocyte antigen-4, ETS = erythroblast transformation-specific, GBM = glioblastoma, GEO = Gene Expression Omnibus, GSEA = gene set enrichment analysis, GSVA = gene set variation analysis, IDH1 = isocitrate dehydrogenase 1, KPS = Karnofsky performance status, MDSCs = myeloid-derived suppressor cells, NK = natural killer, OS = overall survival, PD-1 = programmed death-1, PD-L1 = programmed death ligand-1, TAMs = tumor-associated macrophages, TCGA = The Cancer Genome Atlas, TIM-3 = T cell immunoglobulin mucin-3, Tregs = regulatory T cells, WHO = World Health Organization.

Keywords: biological markers, ELK3, gene targeting, glioma, immunotherapy

1. Introduction
Glioma represents the most prevalent primary brain tumor, accounting for more than 80% of primary malignant central nervous system tumors.[1] Based on the World Health Organization (WHO) classification, gliomas are histologically classified into different tumor types and malignant grades ranging from grade I to grade IV.[2] Despite advances in treatment, the prognosis of patients with gliomas remains poor, especially in glioblastoma (GBM), where the median overall survival (OS) is less than 1 year.[3] Recent advances in biomedical techniques have resulted in the identification of many molecular classifications and biomarkers of glioma. Unfortunately, effective biomarkers to predict prognosis and guide therapeutic strategies are still lacking. Therefore, the establishment of reliable prognostic biomarkers and therapeutic targets in glioma is strongly needed.

The authors have no conflicts of interest to disclose.
The datasets used and analyzed during the current study are available in The Cancer Genome Atlas (TCGA) (https://cancergenome.nih.gov/) and Gene Expression Omnibus (GEO).
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*Department of Neurosurgery, Wuhan Changjiang Shipping General Hospital, Wuhan, China; School of Information Management, Wuhan University, Wuhan, China; Department of Neurosurgery, Zhongnan Hospital of Wuhan University, Wuhan, China; Department of Neurosurgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China.
*Correspondence: Songshan Chai, Department of Neurosurgery, Zhongnan Hospital of Wuhan University, No. 169, Donghu Road, Wuhan, Hubei 430071, China (e-mail: 1303823432@qq.com).
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Immunotherapy targeting immune checkpoints has demonstrated remarkable efficacy in the treatment of various cancers, particularly in renal cell carcinoma, melanoma, and nonsmall-cell lung cancer. The pioneering discovery of lymphatics in the central nervous system raises the hope for the use of immunotherapy for brain tumors. However, most gliomas remain refractory to current immunotherapies. Programmed death ligand-1 (PD-L1), cytotoxic T-lymphocyte antigen-4 (CTLA-4), and T cell immunoglobulin mucin-3 (TIM-3) expressions have been reported to be tightly linked to glioma prognosis and immune responses. Numerous studies have contributed much to improving our current understanding of the intricate interactions between immunity and glioma.

ELK3, also known as erythroblast transformation-specific (ETS)-related protein, Net, or saposin-like protein-2, is a member of the ETS transcription factor family and is differentiated from other ETS family members by its ability to repress transcription. Although ELK3 usually serves as a repressor of gene expression, it can be converted into a transcriptional activator after being phosphorylated by Ras-extracellular signal-regulated kinase signaling. The transcriptional activity of ELK3 has been related to various cellular phenomena, such as vasculogenesis, lymphangiogenesis, and wound healing. Previous studies have demonstrated that ELK3 is overexpressed in various malignancies, such as aggressive breast cancer, prostate cancer, and squamous cell carcinoma, and ELK3 correlates with cancer cell migration, invasion, and chemotherapy resistance. However, the function of ELK3 in glioma is still unknown.

In this study, we explored ELK3 expression profile and its clinical characteristics in glioma using The Cancer Genome Atlas (TCGA) and Gene Expression Omnibus (GEO) datasets. Furthermore, we determined in the TCGA set the extent to which ELK3 expression is associated with inflammatory activities, infiltration of immune cells, and multiple immune checkpoint members. The findings of this study may enhance our understanding of the immunobiology of glioma and provide evidence for potential anti-ELK3 treatment in glioma immunotherapy.

2. Method

2.1. Data collection

GSE50161 RNA microarray data were downloaded from the GEO dataset; the array platform used was Affymetrix-GPL570. The glioma RNA-sequencing data and corresponding clinical information were obtained from the TCGA dataset, and they were analyzed to explore the interaction between ELK3 transcript levels and clinicopathologic characteristics in gliomas. TCGA and GEO belong to public databases. The patients involved in the database have obtained ethical approval. Users can download relevant data for free for research and publish relevant articles. Our study is based on open source data, so there are no ethical issues and other conflicts of interest.

2.2. Bioinformatics analysis

To gain insight into the biological role of ELK3 in glioma pathogenesis, gene set enrichment analysis (GSEA) was used to
identify the biological pathways enriched differentially between low- and high-ELK3 expression tumor groups; 1000 gene set permutations were conducted for each analysis. The gene sets with values of \( P < .05 \) and false discovery rate <0.05 were considered to be enriched. Additionally, gene set variation analysis (GSVA) transformed gene transcript levels into enrichment scores for inflammatory response metagenes. Then, the relationships between ELK3 and these inflammatory metagenes were verified using corr-elogs.

2.3. Statistical analysis
The R programming language 3.6, GraphPad Prism 7.0 (La Jolla, CA), and SPSS 25.0 (IBM Corp., NY) were used for statistical analysis and drawing figures. Descriptive statistics were employed to describe the clinical and molecular features of TCGA glioma patients. The Shapiro–Wilk test was conducted before data analysis that needed normal distribution. Differences in normally distributed variables were evaluated by Student’s \( t \)-test or one-way analysis of variance depending on the number of groups; differences in abnormally distributed variables were assessed using the Kruskal–Wallis test or the Mann–Whitney test as appropriate. Logistic regression analysis was performed to further explore the relationships between ELK3 and clinicopathologic features. In addition, Cox regression analysis and the Kaplan–Meier method were used to assess the prognostic value of ELK3. Canonical correlation analysis was used to explore the correlations between ELK3 expression and inflammatory response metagenes, infiltrating immune cells, or immune checkpoints. All differences were regarded as statistically significant at \( P < .05 \).

3. Results
3.1. ELK3 transcript levels in glioma
By examining the RNA-sequencing data from the TCGA dataset, we found that gliomas had a significantly higher ELK3 mRNA level than nontumor tissues (Fig. 1A, \( P = .002 \)). Moreover, this result was well validated using the GSE50161 array set (Fig. 1B, \( P < .001 \)). Additionally, receiver operating characteristic curves for ELK3 expression and sample type were constructed, and the areas under the curves (AUC) were up to 86.5% and 89.9% \( \times 10^{-5} \) for ELK3 expression and sample type, respectively (Fig. 1C, D). These results were well validated using the GSE50161 array set (Fig. 1B, \( P < .001 \)). Furthermore, this result was reconfirmed using the GEO and TCGA datasets, respectively (Fig. 1C, D). Collectively, these findings indicated that ELK3 may be a diagnostic biomarker for glioma.

3.2. Patient clinical characteristics
The function of ELK3 in glioma was explored based on the TCGA dataset, which includes 1114 glioma samples: 130 oligoastrocytomas, 191 oligodendrogliomas, 194 astrocytomas, 596 GBMs, and 3 without histological confirmation. Among these patients, median age was 52 years; 651 were males and 460 were females. Of 125 samples analyzed for the isocitrate dehydrogenase 1 (IDH1) mutation, 34 (27.2%) samples were wild type, and 91 (72.8%) were mutated. With respect to tumor status, 783 patients (70.3%) had tumors, and 209 (18.8%) were tumor-free. Finally, 51.7% (n = 570) patients were alive at the last follow-up and 539 (48.3%) were dead, while five patients lost contact (Table 1).

3.3. Associations between ELK3 expression and clinicopathologic characteristics
To characterize the ELK3 expression profile, we assessed the association of ELK3 expression with previously accepted predictive and prognostic clinicopathologic factors in gliomas.

3.4. ELK3 predicted poor prognosis of gliomas
To investigate the impact on survival, we examined the prognostic significance of ELK3 using the Kaplan–Meier method. In the TCGA dataset, glioma patients with OS data were divided into low expression and high expression groups according to the cut-off value (median ELK3 expression level). As illustrated in Figure 3, the patients in the high ELK3 expression group had remarkably shorter OS than their low expression counterparts.

The prognostic significance of ELK3 in gliomas was further investigated by univariate and multivariate Cox regression. A total of 371 cases with complete data for all variables were identified and analyzed. Univariate Cox regression analysis revealed that high ELK3 expression was related to poor OS (HR = 1.12, 95% CI 1.09–1.15, \( P < .001 \)). Other clinicopathologic variables, such as age, KPS, tumor status, WHO grade, and histological type, were also significantly correlated with OS (all \( P < .001 \)). In multivariate analysis, ELK3 expression was an independent prognostic variable for OS (HR = 1.05, 95% CI 1.09–1.15, \( P = .002 \)) (Table 3).

Table 1

| Characteristic          | No. of patients (available data) |
|-------------------------|----------------------------------|
| Median age              | 52 y                             |
| Gender                  |                                  |
| Male                    | 651 (58.4%)                      |
| Female                  | 460 (41.3%)                      |
| KPS                     |                                  |
| <80                     | 151 (13.6%)                      |
| ≥80                     | 584 (52.4%)                      |
| IDH1 status             |                                  |
| Mutation                | 91 (8.17%)                       |
| Wild-type               | 34 (3.05%)                       |
| Tumor status            |                                  |
| Tumor free              | 209 (18.8%)                      |
| With tumor              | 783 (70.3%)                      |
| Vital status            |                                  |
| Alive                   | 570 (51.2%)                      |
| Dead                    | 539 (48.4%)                      |
| Grade                   |                                  |
| II                      | 249 (22.4%)                      |
| IV                      | 265 (23.8%)                      |
| GBM                     | 596 (53.5%)                      |
| Histological type       |                                  |
| Oligoastrocytoma        | 130 (11.7%)                      |
| Oligodendroglioma       | 191 (17.2%)                      |
| Astrocytoma             | 194 (17.4%)                      |
| GBM                     | 596 (53.5%)                      |

GBM = glioblastoma, IDH1 = isocitrate dehydrogenase 1, KPS = Karnofsky performance status.
3.5. ELK3-related biological process

GSEA was used to investigate the biological process tightly correlated with ELK3 expression. As illustrated in Table 4 and Figure 4, some signaling pathways related to immune and inflammatory responses, such as B-cell receptor, T-cell receptor, Toll-like receptor, antigen processing and presentation, natural killer cell-mediated cytotoxicity, cytokine-cytokine receptor interaction, and Fc gamma R-mediated phagocytosis, were enriched differentially with the high-ELK3 expression phenotype.

3.6. ELK3-related inflammatory activities

Several well-established metagenes (see Table S1, Supplemental Digital Content, http://links.lww.com/MD/G803, which demonstrates seven inflammatory metagenes comprising 104 genes) representing distinct inflammation and immune response types were chosen to further comprehend the relationships between ELK3 and inflammatory activities. IDH status, WHO grade, histological type, vital status, tumor status, and ELK3 expression of patients were visualized as a heat map. As illustrated in Figure 5A, ELK3 transcript levels were positively related to most inflammatory metagenes in the TCGA dataset except for the IgG metagene. To validate what we found in clusters, GSVA transformed gene ELK3 transcript levels into scores representing enrichment in these metagenes. Corrgrams were formed based on the Pearson r value between ELK3 and inflammatory metagenes. ELK3 expression was positively linked to major histocompatibility complex I, major histocompatibility complex II, signal transducer and activator of transcription 1, interferon, lymphocyte-specific protein tyrosine kinase, and hematopoietic cell-specific kinase metagenes but negatively linked to IgG metagene (Fig. 5B), which was consistent with the aforementioned results.

3.7. Associations between ELK3 expression and infiltrating immune cells

Immune cells are important effectors in inflammatory and immune activities. Immune cells infiltrating tumor tissues play an essential role in regulating glioma prognosis and progression. We evaluated the association between ELK3 and tumor-infiltrating immune cells, including tumor-associated macrophages (TAMs), neutrophils, natural killer (NK) cells, regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), and CD8+ T cells. The specific biomarkers for each type of immune cell are shown in Table S2 (Supplemental Digital Content, http://links.lww.com/MD/G804, which demonstrates the specific biomarkers for each type of immune cell). Canonical correlation analyses showed that ELK3 transcript levels were positively related to all six immune cell-specific markers expression (Fig. 6A), which indicated that gliomas with high ELK3 expression were inclined to present more tumor-infiltrating immune cells than those with low ELK3 expression.
3.8. ELK3 was synergistic with immune checkpoints

Several immune checkpoints that have been evaluated as immunotherapeutic targets in preclinical or clinical studies were analyzed in this analysis, including PD-1 (programmed death-1), PD-L1, TIM-3, B7-H3 (designated B7 homolog 3), and B7-H4 (designated B7 homolog 4), summarized by Wang et al.\[23\] We demonstrated that ELK3 was positively correlated with PD-1, PD-L1, TIM-3, and B7-H3 (Fig. 6B), implying that ELK3 is correlated to the PD-L1/PD-1 pathway and may have an essential role in the immune response.

4. Discussion

In the present study, ELK3 was significantly upregulated in gliomas using the GEO and TCGA datasets. RNA-sequencing data of 1114 glioma samples from the TCGA dataset were obtained and analyzed. ELK3 expression increased with rising WHO grade and was related to prognostic clinicopathologic factors, including age, IDH1 mutation, histological type, vital status, tumor status, and KPS. Among them, KPS was believed to be a risk factor for predicting both mortality and morbidity in glioma patients.\[24\] Moreover, higher expression of ELK3 predicted worse OS in glioma patients. Univariate and multivariate Cox regression revealed that ELK3 may act as a new prognostic biomarker. These findings suggest that ELK3 expression is tightly associated with glioma development and malignant progression.

Through the analysis of the correlation between ELK3 and biological processes using GSEA, we discovered that the expression of ELK3 was closely linked to immune and inflammatory responses. To thoroughly comprehend ELK3-related inflammatory activities, a heatmap involving seven inflammatory metagene was generated and demonstrated that ELK3 expression is positively related to major histocompatibility complex I, major histocompatibility complex II, signal transducer and activator of transcription 1, interferon, lymphocyte-specific protein tyrosine kinase, and hematopoietic cell-specific kinase metagenes was generated and demonstrated that ELK3 expression was positively related to major histocompatibility complex I, major histocompatibility complex II, signal transducer and activator of transcription 1, interferon, lymphocyte-specific protein tyrosine kinase, and hematopoietic cell-specific kinase.

Figure 3. Survival analysis of ELK3 in gliomas from TCGA dataset. Abbreviation: TCGA = The Cancer Genome Atlas.

Table 2

| Variable       | Odds ratio in ELK3 expression | P     |
|----------------|------------------------------|-------|
| Age ≥52 vs <52 | 3.07 (2.23–4.26)             |       |
| Gender         |                              |       |
| Male vs female | 1.16 (0.85–1.57)             | .35   |
| KPS <80 vs ≥80 | 1.56 (0.93–2.65)             | .09   |
| Vital status   |                              |       |
| Dead vs alive  | 3.78 (2.65–5.44)             |       |
| Tumor status   |                              |       |
| With tumor vs tumor free | 2.62 (1.84–3.77) |       |
| Histological type |                            |       |
| GBM vs oligodendroglioma | 15.59 (8.63–29.49) |       |
| GBM vs astrocytoma | 27.80 (15.63–51.93) |       |
| IDH1 status    |                              |       |
| Wild-type vs mutation | 3.35 (1.47–8.10) | .005  |
| Grade          |                              |       |
| III vs II      | 2.87 (1.98–4.19)             |       |
| IV vs II       | 23.17 (13.43–42.00)          |       |

Table 3

| Variable       | Hazard ratio (95% CI) | P     |
|----------------|-----------------------|-------|
| A              |                        |       |
| Age            | 1.07 (1.05–1.08)       | .92   |
| Gender (male)  | 0.98 (0.70–1.38)       |       |
| KPS            | 0.95 (0.94–0.96)       |       |
| Grade (IV)     | 4.66 (3.48–6.25)       |       |
| Tumor status (with tumor) | 37.06 (5.19–265.21) |       |
| Histological type (GBM) | 2.45 (2.00–3.00) |       |
| ELK3 expression | 1.12 (1.09–1.15)       |       |

B

| Variable       | Hazard ratio (95% CI) | P     |
|----------------|-----------------------|-------|
| Age            | 1.05 (1.03–1.06)       |       |
| KPS            | 0.98 (0.97–0.99)       | .004  |
| Tumor status (with tumor) | 22.07 (3.07–158.51) | .002  |
| Histological type (GBM) | 1.55 (1.27–1.90) |       |
| ELK3 expression | 1.05 (1.01–1.09)       | .002  |

CI = confidence interval, GBM = glioblastoma, KPS = Karnofsky performance status, TCGA = The Cancer Genome Atlas.
poor survival. These results suggested that ELK3 may act as a potential cancer therapeutic target.

Glioma cells produce numerous growth factors, chemokines and cytokines, which stimulate the infiltration of a variety of immune cells, including TAMs, neutrophils, NK cells, MDSCs, Tregs, and CD8+ T cells, to the tumor sites. These tumor-infiltrating immune cells constitute the tumor microenvironment that participates in cancer development, metastasis, recurrence, and response to treatment. The immune system could mount immune responses against gliomas, but these responses are insufficient for tumor eradication due to massive immunosuppression within the tumor microenvironment. Hence, modifying the immunosuppressive climate will undoubtedly be an essential component in the treatment of gliomas. In our study, an intriguing novel observation was that ELK3 may be involved in the glioma immune microenvironment. ELK3 transcript levels were positively associated with infiltrating levels of immune cells, such as Tregs, neutrophils, and MDSCs. These cells can be regarded as immunosuppressive cells, showing strong immunosuppressive activities and resulting in adverse prognosis in glioma patients. Certainly, the precise interactions of ELK3 with immunosuppressive cells need to be elucidated by future studies.

Table 4. Gene sets enriched with the high ELK3 expression phenotype.

| Gene set term                                   | Normalized enrichment score | Nominal P-value | FDR q-value |
|------------------------------------------------|-----------------------------|----------------|-------------|
| KEGG_ANTIGEN_PROCESSING_AND_PRESENTATION       | 2.01                        | 0.0053         |             |
| KEGG_B_CELL_RECEPTOR_SIGNALING_PATHWAY         | 1.87                        | 0.0131         |             |
| KEGG_CYTOKINE_CYTOKINE_RECEPTOR_INTERACTION    | 2.01                        | 0.0049         |             |
| KEGG_FC_GAMMA_R_MEDIATED_PHAGOCYTOSIS          | 1.86                        | 0.0124         |             |
| KEGG_JAK_STAT_SIGNALING_PATHWAY                | 1.86                        | 0.0121         |             |
| KEGG_NATURAL_KILLER_CELL_MEDIATED_CYTOTOXICITY | 1.97                        | 0.0067         |             |
| KEGG_PATHWAYS_IN_CANCER                        | 1.70                        | 0.0479         |             |
| KEGG_T_CELL_RECEPTOR_SIGNALING_PATHWAY         | 1.72                        | 0.0436         |             |
| KEGG_TOLL LIKE_RECEPTOR_SIGNALING_PATHWAY      | 1.87                        | 0.0132         |             |

FDR = false discovery rate.

Figure 4. Gene set enrichment analysis (GSEA) identifying biological pathways enriched in the high-ELK3 expression group.
antitumor immunity. Thus, the combination of different immunotherapeutic approaches is expected to benefit glioma treatment. Preclinical studies using murine models with gliomas have shown great benefit with combinatorial immunotherapeutic regimens. For instance, the combination of anti-PD-1 and anti-TIM-3 in the setting of radiation therapy led to regression of murine gliomas, and the combination of PD-L1, CTLA-4, and indoleamine 2,3-dioxygenase blockades resulted in durable survival in 100% of glioma-bearing mice. Successful preclinical studies have prompted clinical studies testing combinatorial therapeutic approaches. A phase II clinical trial (NCT02335918) is assessing the combination of anti-PD-1 and anti-CD27 in patients with glioblastoma. Two more phase II/III clinical trials are evaluating the use of anti-PD-1 in combination with anti-CTLA-4 in the treatment of recurrent glioma (NCT02017717 and NCT02794883). In our study, ELK3 was identified as a potential immunotherapeutic target. We initially investigated the correlation between ELK3 and immune checkpoints and found that ELK3 has a high concordance with immunosuppressive members, such as TIM-3, PD-1, PD-L1, B7-H3, and B7-H4, indicating their synergistic effects in modulating glioma immune microenvironment. For the association between ELK3 expression and immune infiltration and checkpoint receptor expression, we propose the following hypotheses: (1) ELK3 may promote immune escape through IFγ-PD-L1, (2) ELK3 may improve the expression of B7-H3 and B7-H4 favored an immunosuppressive microenvironment by promoting the production of IL-10 and TGF-β1. These findings provide new combinatorial therapeutic opportunities for gliomas. The combination therapy of immune checkpoints and ELK3 may contribute to overcoming the shortcomings associated with blockading immune checkpoints alone.

There are some limitations in our current study. First, this study was based on a retrospective analysis of data obtained from TCGA. Therefore, selection bias was inevitable. Second, because of the lack of integrated clinical data in TCGA, the sample size was relatively small in the Cox regression analysis. Third, due to the small number of healthy control samples, additional studies with balanced sample sizes are required. Fourth, mRNA expression does not necessarily predict protein abundance since the transcription process can be altered in cancers. Thus, future studies assessing ELK3 protein levels will be necessary to confirm the essential role of ELK3 in gliomas. Certainly, laboratory studies to explain the detailed mechanisms of increased ELK3 expression and clarify its correlation with glioma immunomodulation are also required.

5. Conclusions

In summary, our study first found that ELK3 was upregulated in gliomas and that its high-level expression was significantly correlated with advanced clinicopathological characteristics and poor outcome. Moreover, ELK3 was related to immune and inflammatory responses and synergistic with several immunosuppressive checkpoint members. Taken together, these findings imply that ELK3 may act as a novel prognostic biomarker and a potential immunotherapeutic target, which may amplify the therapeutic efficacy of immunotherapy for glioma when combined with immune checkpoint inhibitors.
Figure 6. Relationships between ELK3 and immune cell-specific markers (A); correlations of ELK3 with immune checkpoints (B).
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