·论　著·

STK40在脑胶质瘤中的表达及其临床意义的生信分析

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【摘要】**目的** 探讨丝氨酸/酸酸蛋白激酶40(STK40)在脑胶质瘤中的表达及其临床意义。**方法** 计算机检索GEPIA数据库，运用生物信息学方法分析STK40在胶质瘤组织及正常脑组织中的表达差异；同时，检索CGGA数据库中693例脑胶质瘤的基因信息及临床资料，运用Kaplan−Meier生存曲线分析STK40表达水平与脑胶质瘤生存预后的关系；采用多因素Cox比例回归风险模型分析脑胶质瘤生存预后的影响因素。**结果** GEPIA数据库分析显示，胶质母细胞瘤组织STK40表达水平较正常脑组织明显增高(P<0.05)。STK40表达水平与胶质瘤病理级别呈正相关，随胶质瘤病理级别增高，STK40表达水平明显增高(P<0.0001)。多因素Cox风险比例回归模型分析结果显示，STK40高表达是脑胶质瘤生存预后不良的独立危险因素(P<0.05)。Kaplan−Meier生存曲线分析显示，STK40高表达组中位总生存期较低表达组明显缩短(P<0.0001)；而且STK40高表达明显降低胶质瘤放/化疗的效果(P<0.0001)。Pearson相关性分析显示，ERK下游产物SRF与STK40呈明显正相关(r=0.45；P<0.0001)，JNK下游产物ATF2与STK40表达水平呈明显负相关(r=−0.167；P<0.0001)。**结论** 胶质瘤STK40呈高表达，与病人生存预后不良有关，其作用机制可能与ERK/MAPK及JNK/MAPK信号通路有关。

【关键词】脑胶质瘤；丝氨酸/酸酸激酶40；基因表达；生信分析

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Expression of STK40 in human glioma and and its clinical significance based on bioinformatics analysis

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【**Abstract**】 **Objective** To investigate the expression of serine/threonine protein kinase (STK40) in gliomas and its clinical significance. **Methods** The GEPIA database was used to analyze the expression difference of STK40 in glioma tissues and normal brain tissues. Bioinformatics methods were used to analyze the gene information and clinical data of 693 patients with glioma obtained from the CGGA database. Kaplan−Meier survival curve was used to analyze the relationship between STK40 expression and survival time of patients with glioma. Multivariate Cox risk proportional regression model was used to analyze the risk factors of the survival prognosis of patients with glioma. **Results** The GEPIA database analysis showed that the STK40 expression level in the glioblastoma tissues was significantly higher than the normal brain tissues (P<0.05). The expression level of STK40 was positively correlated with the pathological grade of glioma, and the expression level of STK40 increased significantly with the increase of the pathological grade of glioma (P<0.0001). Multivariate Cox hazard proportional regression model analysis showed that high expression of STK40 was an independent risk factor for poor survival prognosis of glioma patients (P<0.05). Kaplan−Meier survival curve analysis showed that the median overall survival of the glioma patients with high expression of STK40 was significantly shorter than those with low expression of STK40 (P<0.0001); the high STK40 expression significantly reduced the curative effect of radiotherapy/chemotherapy on glioma (P<0.0001). Pearson correlation analysis showed that SRF, the downstream product of ERK, was positively correlated with STK40 (r=0.45; P<0.0001), and ATF2, the downstream product of JNK, was negatively correlated with the expression level of STK40 (r=−0.167; P<0.0001). **Conclusions** The high expression of STK40 in glioma is associated with poor survival prognosis of glioma patients, and its mechanism may be related to the ERK/MAPK and JNK/MAPK signaling pathways.

【**Key words**】 Glioma; Serine/threonine protein kinase 40; STK40; Gene expression; Bioinformatics methods

胶质瘤是颅内最常见的原发性肿瘤[1]，恶性程度高，预后差[2,3]。目前标准的治疗以手术为主，辅以放疗和化疗(替莫唑胺)，但术后复发率高[4]。目前，靶向治疗是一种有潜力的治疗肿瘤的方法，因此，寻找新的治疗靶点，有助于开发靶向药物、改善病人的预后。丝氨酸/苏氨酸蛋白激酶(serine/threonine proteinkinase，STK)与多种恶性肿瘤有关，例如慢性淋巴细胞白血病[6]、结直肠癌[7]、黑色素瘤[8]、乳腺癌[9]

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等。有文献报道STK40高表达是低级别胶质瘤预后的独立影响因素[10]。本文采用生信分析方法探讨STK40在胶质瘤中的表达及意义。

1 资料和方法

1.1 数据库检索 运用GEPIA数据库(整合肿瘤细胞全基因组信息的TGGA数据库和正常组织全基因信息的GTEx数据库),分析STK40在胶质瘤组织及正常脑组织中的表达差异。检索CGGA数据库(www.cgga.org.cn),收集胶质瘤693例,分析相关基因信息及临床资料,其中36例未追踪到生存时间;追踪到总生存时间的657例中,男374例,女283例;年龄11~76岁;WHO分级Ⅱ级172例,Ⅲ级284例,Ⅳ级237例;初发404例,复发253例。

1.2 统计学方法 采用SPSS 26软件和GraphPad-Prism9软件进行统计学分析;计量资料用$\bar{x}\pm s$表示,采用t检验;计数资料采用χ^2检验;利用多因素Cox比例回归风险模型分析生存影响因素;采用Pearson相关系数分析相关性;应用Kaplan-Meier法进行生存分析;P<0.05为差异有统计学意义。

2 结 果

2.1 胶质瘤STK40表达变化 胶质母细胞瘤STK40表达水平明显高于正常脑组织(P<0.05,图1)。

2.2 STK40表达与胶质瘤病理级别的关系 STK40表达水平与胶质瘤病理级别呈正相关,随胶质瘤病理级别增高,STK40表达水平明显增高(P<0.0001,图2)。对于WHO分级Ⅱ级、Ⅲ级胶质瘤,复发胶质瘤STK40表达水平较初发胶质瘤明显增高(P<0.0001;图2);而对于WHO分级Ⅳ级胶质瘤,复发与初发无明显差异(P>0.05;图2)。

2.3 STK40表达水平与胶质瘤病理类型的关系 按2021年WHO中枢神经系统肿瘤分型,星型细胞瘤(IDH突变型)、少突胶质细胞瘤(IDH突变型和1p/19q共缺失型)和胶质母细胞肿瘤(IDH野生型);结果表明,星形细胞瘤和胶质母细胞瘤STK40表达水平明显高于少突胶质细胞瘤(P<0.0001,图3)。

2.4 脑胶质瘤生存预后的影响因素 多因素Cox风险比例回归模型分析结果显示,STK40表达水平、年龄、IDH突变及1p/19q联合共缺失是脑胶质瘤生存预后的独立影响因素(P<0.05;表1)。

2.5 STK40表达水平与脑胶质瘤生存预后的关系 Kaplan-Meier生存曲线分析显示,以STK40表达水平中位数为界限,分为高表达组和低表达组,结果表明STK40低表达组中位总生存期明显长于高表达组(P<0.0001;图4)。

2.6 STK40表达水平与放疗、化疗的疗效的关系 接受化疗(以替莫唑胺为主)或放疗的脑胶质瘤,STK40低表达组生存时间均明显长于高表达组(P<0.0001;图5)。

2.7 STK40表达水平与ERK/MAPK信号通路、JNK/MAPK的相关性 Pearson相关性分析显示,ERK下游产物SRF与STK40呈明显正相关(r=0.45; P<0.0001),JNK下游产物ATF2与STK40表达水平呈明显负相关(r=-0.167;P<0.0001)。

3 讨 论

STK存在于各类真核细胞中,其序列结构呈高度保守。研究表明STK过表达可能与脑胶质瘤的进

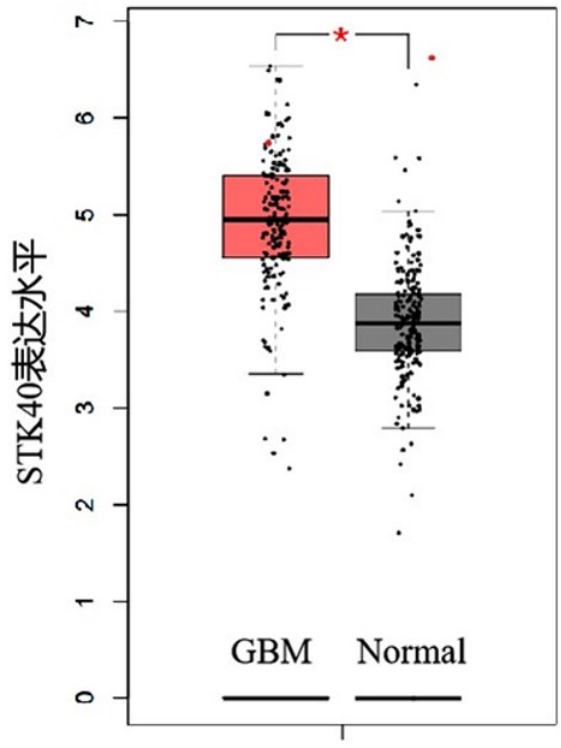

图1 STK40在GBM和正常组织中的表达(来自GEPIA)
GBM. 胶质母细胞瘤

表1 脑胶质瘤生存预后影响因素的多因素Cox比例回归风险模型分析

危险因素	风险比	95%置信区间	P值
STK40高表达	1.988	1.511~2.616	<0.0001
男性	1.040	0.835~1.295	0.729
年龄≥50岁	1.464	1.152~1.861	0.002
IDH突变	1.871	1.459~2.399	<0.0001
1p/19q共缺失	0.574	0.385~0.855	0.006

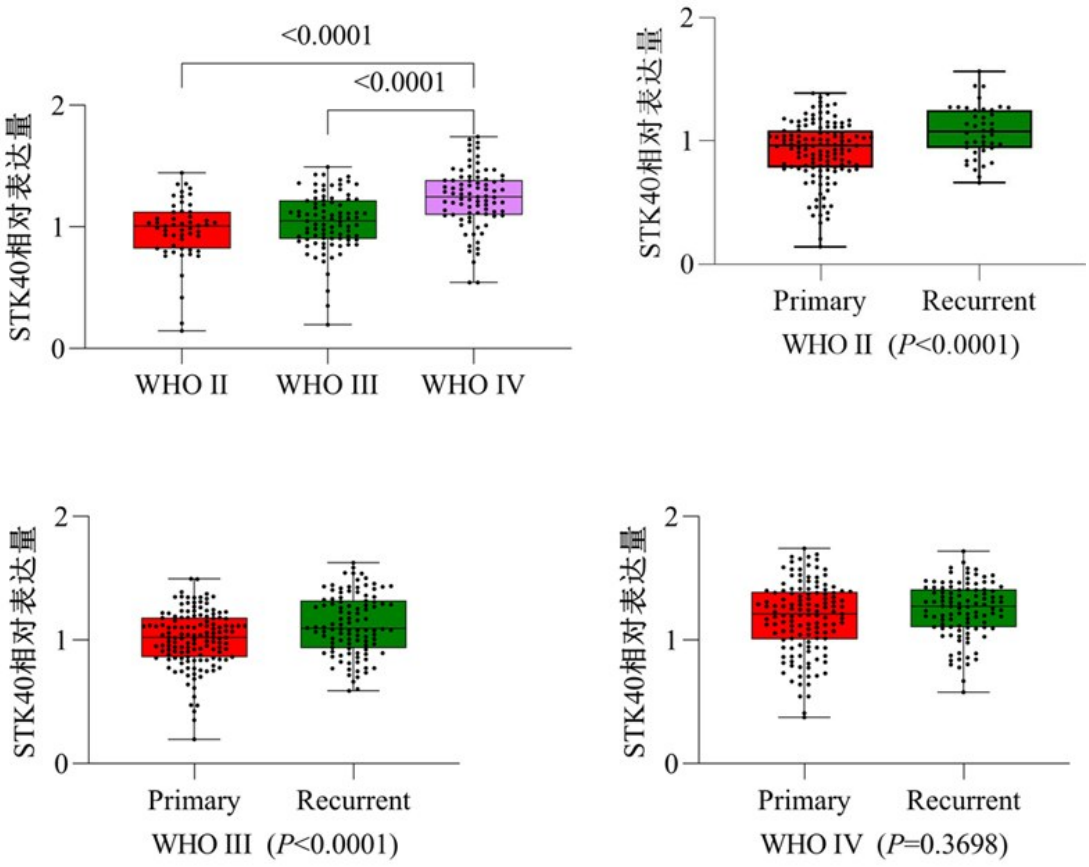

图2 STK40表达与胶质瘤病理级别的关系

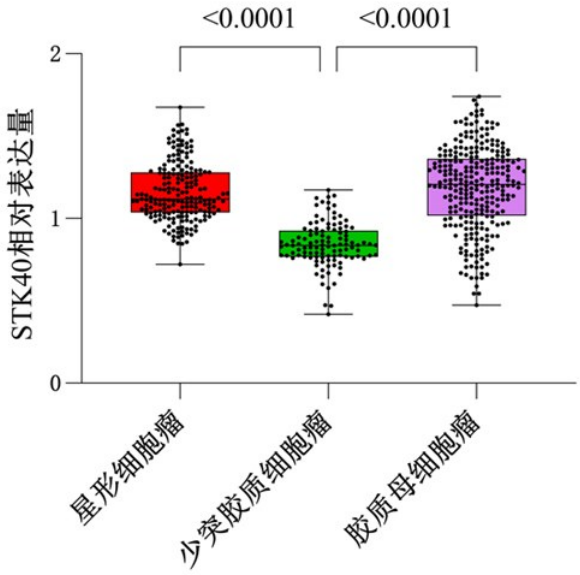

图3 STK40表达水平与胶质瘤病理类型的关系

展有关[11,12]。本文分析CGGA数据库中657例脑胶质瘤的临床资料，发现STK40在脑胶质瘤中呈高表达，且病理级别越高，表达水平越高；STK40表达水平与胶质瘤放化疗敏感性有关；STK40表达水平越高，胶质瘤病人预后越差。

本文发现ERK下游产物SRF与STK40呈明显正相关（r=0.45；P<0.0001），JNK下游产物ATF2与STK40表达水平呈明显负相关（r=−0.167；P<0.0001）。提示STK40的作用机制可能与ERK/MAPK、JNK/MAPK信号通路有关。研究发现，STK40可提高MAPK信号通路调控细胞增殖、分化与凋亡[13~15]。因此，STK40可能通过调控MAPK信号通路促进胶质瘤增殖，但具体机制仍需深入研究。

综上所述，本文结果显示STK40表达水平是影响胶质瘤生存预后的独立影响因素，STK40可能是胶质瘤靶向治疗的潜在靶点。

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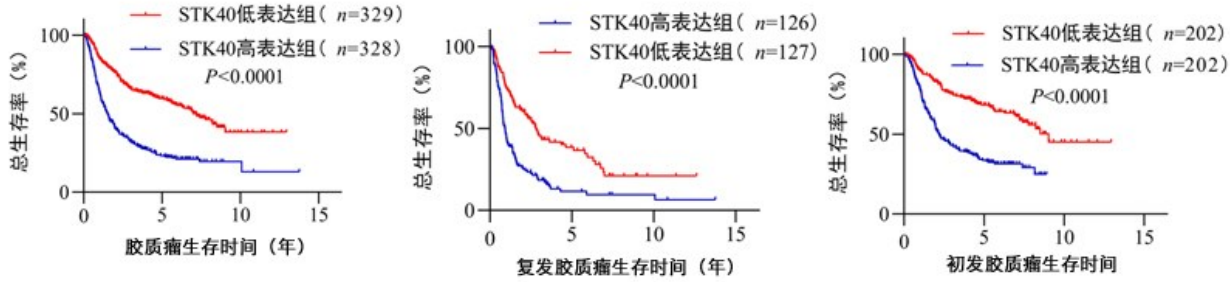

图4 生存曲线分析STK40表达水平与胶质瘤生存预后的关系

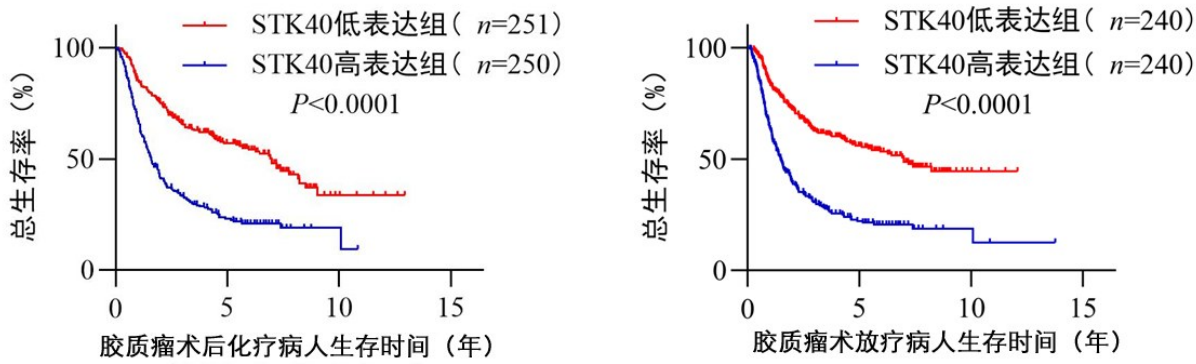

图5 生存曲线分析STK40表达水平与胶质瘤放化疗敏感性的关系

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