·论　著·

ITGA4基因在脑胶质瘤中的表达及临床意义

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【摘要】**目的** 探讨整合素α4(ITGA4)基因在脑胶质瘤中的表达与临床意义。**方法** 计算机检索CGGA数据库获取mRNAseq-325数据集中325例脑胶质瘤的转录组测序(RNA-seq)数据及临床资料,并用mRNAseq-693数据集中693例脑胶质瘤进行验证。**结果** 胶质瘤ITGA4基因呈高表达(P<0.05),与胶质瘤IDH基因型、1p/19q共缺失状态、WHO病理分级有关(P<0.05),与胶质瘤MGMT启动子甲基化状态无明显关系(P>0.05)。多因素Cox回归分析显示,ITGA4高表达是胶质瘤生存预后不良的独立危险因素(P<0.05)。生存曲线分析显示,ITGA4高表达胶质瘤病人生存期明显缩短(P<0.05)。GO分析和KEGG分析显示,ITGA4基因调控的生物过程包括细胞粘附、血管生成及细胞迁移等,主要调控PI3K/AKT信号通路。**结论** 我们的结果提示胶质瘤ITGA4呈高表达,与胶质瘤不良生存预后密切相关,主要调控PI3K/AKT信号通路。

【关键词】胶质瘤;整合素α4(ITGA4);基因表达;生信分析

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Expression of integrin α4 gene in human brain gliomas and its clinical significance based on bioinformatics analysis

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【**Abstract**】 **Objective** To investigate the expression of integrin α4 (ITGA4) gene in human brain gliomas and its clinical significance. **Methods** The transcriptional sequencing (RNA-seq) data and clinical data of 325 patients with gliomas in mRNAseq-325 dataset were downloaded from CGGA database, and 693 patients with gliomas in mRNAseq-693 dataset were used to verified. **Results** ITGA4 gene was highly expressed in human brain gliomas (P<0.05), which was related to IDH genotype, 1p/19q codeletion status, and WHO pathological grade (P<0.05), and was not relatted to MGMT promoter methylation status (P>0.05). Multivariate Cox regression analysis showed that high expression of ITGA4 was an independent risk factor for poor survival prognosis of glioma patients (P<0.05), and survival curve analysis showed that the survival time of glioma patients with high ITGA4 expression was significantly shortened (P<0.05). GO and KEGG analyses showed that ITGA4 gene were involved in biological processes including cell adhesion, angiogenesis, and cell migration, and mainly involved in the PI3K/AKT signaling pathway. **Conclusions** Our results suggest that ITGA4 is highly expressed in gliomas, which is closely related to the poor survival prognoses of glioma patients. ITGA4 mainly regulates the PI3K/AKT signaling pathway.

【**Key words**】Glioma; Integrin α4 (ITGA4); Gene expression; Bioinformatics analysis

胶质瘤是中枢神经系统最常见的恶性肿瘤,复发率、病死率均较高[1]。目前,胶质瘤的临床一线治疗是手术联合术后放化疗,但并未取得令人满意的疗效[2]。近些年,随着精准医学的发展,靶向治疗在各种癌症中的优势逐渐突显[3],但靶向治疗在胶质瘤的治疗方面应用比较局限。寻找与脑胶质瘤发生、发展相关的分子标志物,对预测脑胶质瘤的预后以及提供治疗靶点尤为重要。整合素是由α链和β链组成的一种外源二聚体集成膜蛋白[4]。文献报道,整合素α4(integrin α4,ITGA4)与多种癌症存在相关性[5~8]。本文通过生物信息学方法分析脑胶质瘤ITGA4的表达情况及其临床意义。

1 资料与方法

1.1 数据收集　胶质瘤病人基因信息及临床资料来自CGGA数据库(www.cgga.org.cn)[9~11]及GEPIA数据库(http://gepia.cancer-pku.cn/)[12]。GEPIA数据库分析ITGA4在胶质瘤与正常脑组织表达差异;下载CGGA数据库mRNAseq-325和mRNAseq-693数据集,共包含1 018例胶质瘤,其中男601例,女417例;年龄8~79岁;WHO分级Ⅱ级291例,Ⅲ级334例,Ⅳ

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级388例，未明确分级5例；异柠檬酸脱氢酶（isocitrate dehydrogenase，IDH）野生型435例，突变型531例，未明确52例；1p/19q共缺失型212例，非共缺失型728例，未明确78例；O6-甲基鸟嘌呤-DNA甲基转移酶（O6-methyl guanine DNA methyltransferase，MGMT）启动子甲基化472例，非甲基化376例，未明确170例。

1.2 基因功能富集分析 Person相关系数分析ITGA4与其他基因的相关性，筛选与ITGA4呈显著正相关的前三百个基因（r在0.56~0.82；P<0.0001），并在DAVID数据库（https://david.ncifcrf.gov/）进行GO富集分析和KEGG通路分析。

1.3 统计学方法 选择GraphPad Prism9、R4.2.1及SPSS 26.0软件进行分析；非正态分布计量资料使用Mann Whitney U检验和Kruskal Wallis H检验；采用Cox回归分析生存预后的影响因子；采用Kaplan-Meier生存曲线进行生存分析；以P<0.05为差异有统计学意义。

2 结 果

2.1 胶质瘤ITGA4的表达 胶质母细胞瘤（glioblastoma，multiformeGBM）组织ITGA4表达水平显著高于正常脑组织（P<0.05，图1）。

2.2 胶质瘤ITGA4表达与临床特征的关系 mRNAseq-325和mRNAseq-693数据集分析显示，胶质瘤WHO分级越高，ITGA4表达水平越高（P<0.05；图2A、2E）；IDH野生型胶质瘤ITGA4表达水平较突变型胶质瘤明显增高（P<0.05；图2B、2F）；1p/19q非共缺失胶质瘤ITGA4表达水平较共缺失胶质瘤明显增高（P<0.05；图2C、2G）。胶质瘤ITGA4表达水平与MGMT甲基化水平无明显关系（P>0.05；图2D、2H）。

2.3 胶质瘤生存预后的影响因素 应用mRNAseq-325数据集进行Cox回归分析显示，WHO分级高、ITGA4高表达是胶质瘤生存预后不良的独立危险因素（P<0.05，表1），而术后化疗、1p/19q共缺失是胶质瘤生存预后的有益因素（P<0.05，表1）。应用mRNAseq-693数据集进行Cox回归分析显示WHO分级高、ITGA4高表达是胶质瘤生存预后不良的独立危险因素（P<0.05，表2），而术后化疗、IDH突变、1p/19q共缺失是胶质瘤生存预后的有益因素（P<0.05，表2）。

2.4 ITGA4表达水平与胶质瘤生存预后的关系 以ITGA4表达水平中位数为界分为高表达组和低表达组，生存曲线分析显示，mRNAseq-325数据集中ITGA4高表达组中位总生存期显著低于低表达组（P<0.0001；图6A）；mRNAseq-693数据集中高表达组中位总生存期显著低于低表达组（P<0.0001；图6B）。

2.5 ITGA4的生物学功能 GO分析和KEGG分析显示，ITGA4最相关的生物过程包括细胞粘附、血管生成及细胞迁移等，细胞成分是黏着斑、膜的组成部分等，分子功能是整合素结合与蛋白质结合等；ITGA4主要参与PI3K/AKT信号通路和局灶性黏连通路。

3 讨 论

研究表明，整合素在肿瘤进展中发挥关键作用，其功能或表达的改变促进肿瘤进展[13]。ITGA4为整合素家族的成员之一，与多种癌症发生发展密切相关[5~7,14]。本文首先分析GEPIA数据库中ITGA4在正常组织和胶质瘤组织之间的表达差异，结果表明胶质瘤组织ITGA4表达水平显著增高；应用CGGA数据库中mRNAseq-325数据集和mRNAseq-693数据集进一步分析显示，胶质瘤ITGA4表达与胶质瘤IDH基因型、1p/19q共缺失状态、WHO病理分级有关

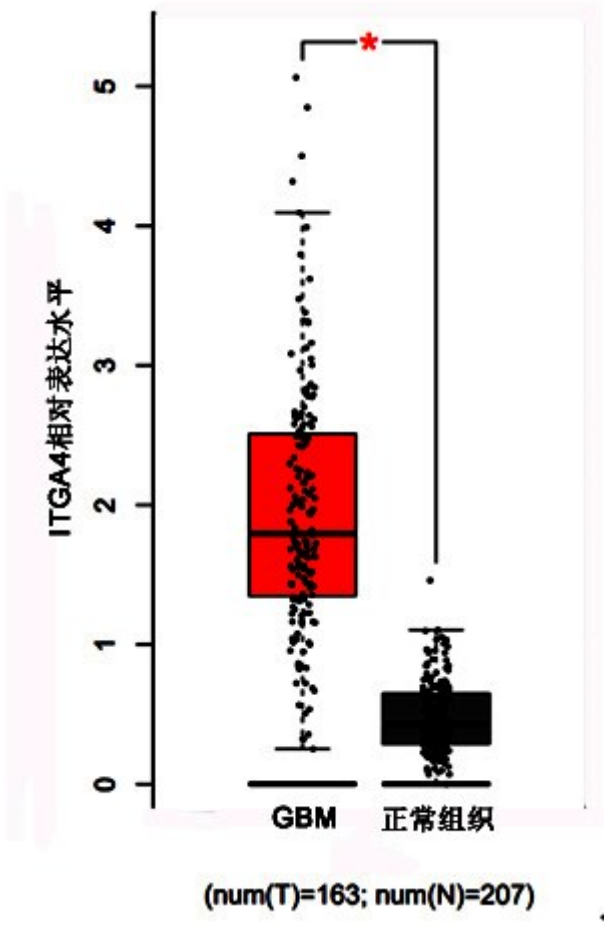

图1 ITGA4在GBM和正常组织中的表达

* P<0.05；GBM. 胶质母细胞瘤

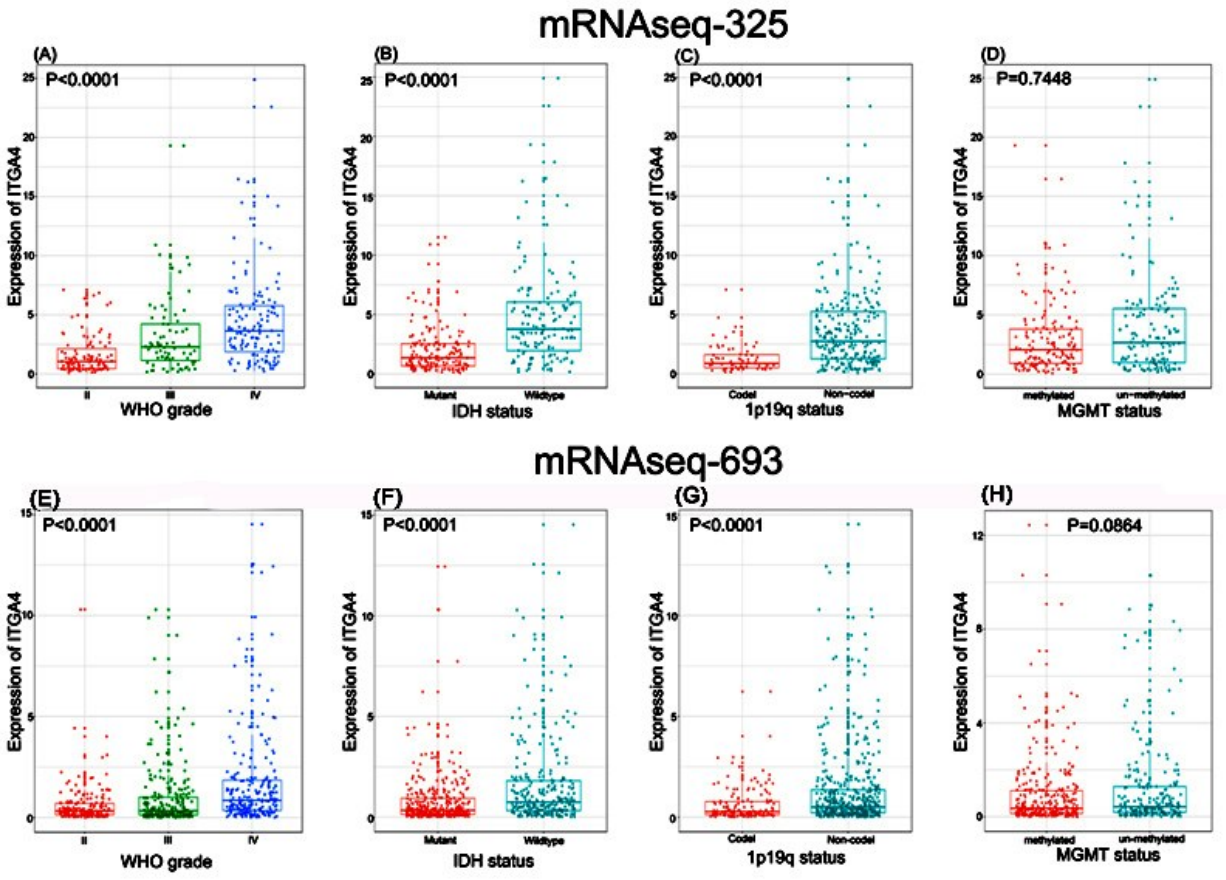

图2 胶质瘤ITGA4表达与临床特征的关系

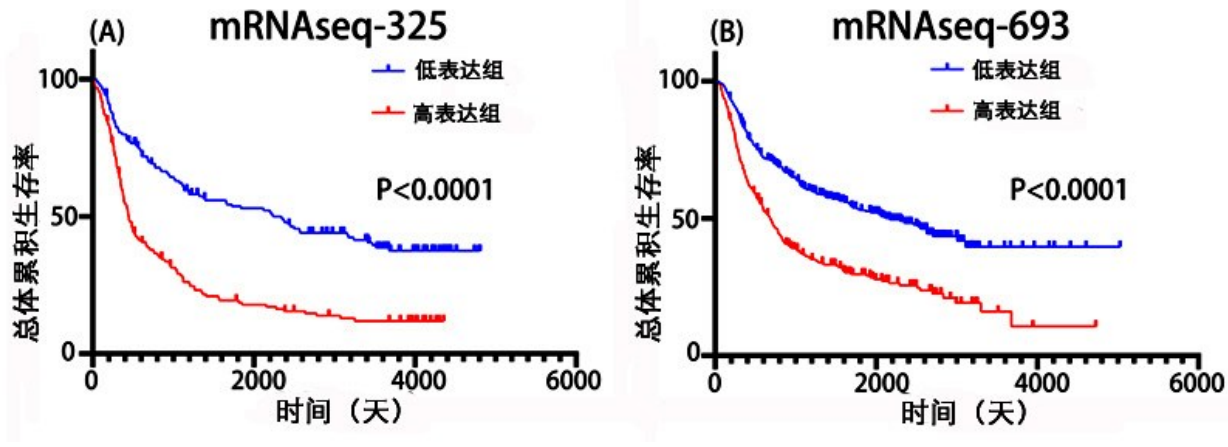

图3 生存曲线分析ITGA4表达水平与脑胶质瘤生存预后的关系

（P<0.05），而与胶质瘤MGMT甲基化水平无明显关系（P>0.05）；多因素Cox回归分析显示，ITGA4高表达是胶质瘤生存预后不良的独立危险因素（P<0.05）；生存曲线分析显示，ITGA4高表达胶质瘤病人生存期明显缩短（P<0.05）；GO分析和KEGG分析显示，ITGA4基因调控的生物过程包括细胞粘附、血管生成及细胞迁移等，主要调控PI3K/AKT信号通路。PI3K/AKT信号通路是癌症中最常激活的信号转导通路之一[15]。这提示ITGA4可能通过PI3K/AKT信号通路影响胶质瘤的发生与发展过程。有文献报道，ITGA4可通过激活PI3K/AKT通路调控胰腺癌的发生与发展[16]；上调ITGA4的表达可激活磷酸化的PI3K和AKT，导致细胞凋亡减少，缓解青光眼[17]。

总之，本文结果提示ITGA4可能在胶质瘤进展过程中发挥重要作用，可能是胶质瘤独立的预后预测因子、潜在的治疗靶点。

表1 mRNAseq-325数据集分析脑胶质瘤总体生存预后不良的危险因素

危险因素	单因素分析			多因素分析		
	风险比	95.0%置信区间	*P*值	风险比	95.0%置信区间	P值
WHO分级高	2.911	2.416~3.507	<0.001	2.486	1.992~3.101	<0.001
性别	0.941	0.716~1.236	0.660			
年龄	1.033	1.020~1.046	<0.001	1.012	0.999~1.024	0.076
术后放疗	0.632	0.457~0.872	0.005	0.807	0.568~1.145	0.229
术后化疗	1.445	1.078~1.937	0.014	0.706	0.510~0.978	0.036
IDH突变	0.355	0.269~0.468	<0.001	1.126	0.785~1.614	0.519
1p19q共缺失	0.170	0.104~0.277	<0.001	0.312	0.183~0.532	<0.001
MGMT甲基化	0.830	0.632~1.089	0.178			
ITGA4高表达	1.139	1.105~1.174	<0.001	1.055	1.013~1.098	0.010

表2 mRNAseq-693数据集分析脑胶质瘤总体生存预后不良的危险因素

危险因素	单因素分析			多因素分析		
	风险比	95.0%置信区间	*P*值	风险比	95.0%置信区间	*P*值
WHO分级高	2.666	2.303~3.087	<0.001	2.008	1.641~2.459	<0.001
性别	1.061	0.868~1.296	0.564			
年龄	1.026	1.018~1.035	<0.001	1.008	0.999~1.017	0.096
术后放疗	1.241	0.953~1.615	0.109			
术后化疗	1.242	0.974~1.586	0.081			
IDH突变	0.323	0.262~0.399	<0.001	0.733	0.543~0.988	0.042
1p19q共缺失	0.268	0.193~0.372	<0.001	0.439	0.293~0.658	<0.001
MGMT甲基化	0.795	0.639~0.990	0.041	0.898	0.706~1.142	0.381
ITGA4高表达	1.174	1.128~1.222	<0.001	1.069	1.004~1.138	0.037

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