

脑胶质瘤组织中 YTHDF2, UBXN1 的表达及其对预后的评估价值

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摘要: 目的 研究脑胶质瘤组织中 YTH 结构域 N6-甲基腺嘌呤 RNA 结合蛋白 2 (YTH domain N6-methyladenine RNA binding protein 2, YTHDF2), UBX 结构域蛋白 1 (UBX domain protein 1, UBXN1) 的表达及预后评估价值。方法 选取 2017 年 2 月~2018 年 2 月青岛市胶州中心医院诊治的 92 例脑胶质瘤患者。免疫组织化学检测组织 YTHDF2, UBXN1 表达。相关性采用 Spearman 秩相关分析。Kaplan-Meier 曲线分析 YTHDF2, UBXN1 表达与脑胶质瘤患者预后的影响。COX 分析脑胶质瘤患者预后影响因素。结果 相比于癌旁组织, 脑胶质瘤中 YTHDF2 (65.22% vs 15.22%) 阳性率较高, UBXN1 (26.09% vs 73.91%) 的阳性率较低, 差异具有统计学意义 ($\chi^2=47.831$, 42.087, 均 $P < 0.05$)。Spearman 秩相关分析, 脑胶质瘤中 YTHDF2 与 UBXN1 表达呈负相关 ($r = -0.712$, $P < 0.05$)。相比于肿瘤直径 $< 3\text{cm}$, WHO 分级 I~II 级, 肿瘤直径 $\geq 3\text{cm}$ 和 WHO 分级 III 级脑胶质瘤组织中 YTHDF2 (75.47% vs 51.28%, 65.22% vs 50.00%) 阳性率较高, 而 UBXN1 (15.09% vs 41.03%, 11.11% vs 47.37%) 阳性率较低, 差异具有统计学意义 ($\chi^2=5.795$, 6.609; 7.835, 15.207, 均 $P < 0.05$)。YTHDF2 阳性组五年总生存率低于阴性组 [28.33% (17/60) vs 62.50% (20/32)], UBXN1 阳性组五年总生存率高于阴性组 [66.67% (16/24) vs 30.88% (21/68)], 差异具有统计学意义 (Log-Rank $\chi^2=12.870$, 7.665, 均 $P < 0.05$)。YTHDF2 阳性 (HR=2.427, 95%CI: 1.426 ~ 4.569)、UBXN1 阴性 (HR=1.740, 95%CI: 1.121 ~ 2.568)、WHO 分级 III 级 (HR=2.671, 95%CI: 1.160 ~ 6.012) 及肿瘤直径 $\geq 3\text{cm}$ (HR=1.628, 95%CI: 1.017 ~ 2.592) 是胶质瘤患者不良预后的危险因素。结论 脑胶质瘤组织中 YTHDF2 升高, UBXN1 降低, 两者与 WHO 分级及肿瘤直径有关。YTHDF2 和 UBXN1 是评估脑胶质瘤患者预后的独立因素。

关键词: 脑胶质瘤; YTH 结构域 N6-甲基腺嘌呤 RNA 结合蛋白 2; UBX 结构域蛋白 1

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Expression of YTHDF2 and UBXN1 in Gliomas and Their Prognostic Value

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Abstract: Objective This study aims to investigate the expression of YTH domain N6-methyladenine RNA binding protein 2 (YTHDF2) and UBX domain protein 1 (UBXN1) in glioma tissue and their prognostic value. **Methods** A total of 92 glioma cases that underwent surgical treatment in Qingdao Jiaozhou Central Hospital from February 2017 to February 2018 were included. Immunohistochemistry was used to detect YTHDF2 and UBXN1 expression. Spearman rank correlation analysis was conducted. Kaplan-Meier survival curves were plotted to analyze the association between YTHDF2, UBXN1 expression and prognosis in glioma patients. COX analysis was used to determine the prognostic factors affecting glioma patients. **Results** Compared with adjacent tissues, the positivity rate of YTHDF2 (65.22% vs 15.22%) was significantly higher in gliomas, while the positivity rate of UBXN1 (26.09% vs 73.91%) was lower, and differences were statistically significant ($\chi^2=47.831$, 42.087, all $P < 0.05$). Spearman rank correlation analysis, showed a negative correlation between YTHDF2 and UBXN1 expression in gliomas ($r = -0.712$, $P < 0.05$). Compared with tumors diameter $< 3\text{cm}$ and WHO grades I to II, YTHDF2 (75.47% vs 51.28%, 65.22% vs 50.00%) had a higher positivity rate in glioma tissues with tumor diameter $\geq 3\text{cm}$ and WHO grade III, while UBXN1 (15.09% vs 41.03%, 11.11% vs 47.37%) had a lower positivity rate, and differences were statistically significant ($\chi^2=5.795$, 6.609; 7.835, 15.207, all $P < 0.05$). The five-year overall survival rate of YTHDF2 positive group was lower than that of negative group [28.33% (17/60) vs 62.50% (20/32)], while the five-year overall survival rate of UBXN1 positive group was higher than that of negative group [66.67% (16/24) vs 30.88% (21/68)], and the differences were statistically significant (Log-Rank $\chi^2=12.870$, 7.665, all $P < 0.05$). YTHDF2 positive (HR=2.427, 95%CI: 1.426 ~ 4.569),

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UBXN1 negative (HR=1.740, 95%CI: 1.121 ~ 2.568), WHO grade III (HR=2.671, 95%CI: 1.160 ~ 6.012) and tumor diameter ≥ 3 cm (HR=1.628, 95%CI: 1.017 ~ 2.592) were risk factors for poor survival prognosis in glioma patients.

Conclusion YTHDF2 increased and UBXN1 decreased in glioma tissues, both of which are related to WHO grading and tumor diameter, and they are independent factors for evaluating the prognosis of glioma patients.

Keywords: glioma; YTH domain N6-methyladenine RNA binding protein 2; UBX domain protein 1

脑胶质瘤(glioma)是常见的中枢神经恶性肿瘤,发病率和死亡率均较高^[1]。脑胶质瘤的治疗包括手术、放化疗及靶向治疗等多学科综合治疗为主,但肿瘤易出现复发转移,患者远期生存预后不佳^[2]。YTH结构域N6-甲基腺嘌呤RNA结合蛋白2(YTH domain-containing family protein 2, YTHDF2)属于YTH结构域超家族成员,能识别并结合N6甲基腺苷(N6-methyladenosine,m6A)修饰的mRNA,调控mRNA的稳定性及细胞信号转导^[3]。研究表明,YTHDF2促进肿瘤抑制因子组氨酸磷酸酶mRNA降解,磷酸化激活AKT,诱导前列腺癌细胞增殖和转移^[4]。UBX结构域蛋白1(UBX domain containing protein 1, UBXN1)属于泛素相关结构域家族成员,参与调控泛素蛋白酶体途径及内质网相关降解过程^[5]。研究表明,乳腺癌、前列腺癌中UBXN1表达降低,导致乳腺癌易感基因1的过度激活,促进癌细胞的增殖及侵袭^[6-7]。目前脑胶质瘤中YTHDF2, UBXN1的表达及临床意义尚不清楚。本研究旨在研究脑胶质瘤中YTHDF2, UBXN1表达的预后评估价值。

1 材料与方法

1.1 研究对象 留取2017年2月~2018年2月青岛市胶州中心医院确诊为脑胶质瘤的92例患者的临床资料。纳入标准:①均接受脑胶质瘤切除术手术治疗,既往无放化疗治疗;②初次诊治,病历资料完整,无手术禁忌症;③病理学确诊为脑胶质瘤;④患者及家属已签署研究的知情同意书。排除标准:①同时并发其他部位的恶性肿瘤;②并发严重基础性疾病,或心、肺、肝和肾等脏器功能障碍;③围手术期死亡或随访中因其它原因导致死亡;④年龄 < 18 岁。男性51例,女性41例,年龄32~79(56.23 \pm 6.14)岁;病理类型:星形胶质细胞瘤38例,少突胶质细胞瘤34例,室管膜瘤20例;肿瘤直径 ≥ 3 cm 53例, < 3 cm 39例;侵犯脑叶数: < 2 个44例, ≥ 2 个48例;WHO分级:I~II级($n=38$),III级($n=54$)。该研究通过医院伦理相关要求,并获得批准(批准文号:M20230042)。

1.2 仪器与试剂 免疫组织化学试剂盒(北京中杉金桥公司,型号PV9000);YTHDF2, UBXN1兔单克隆抗体(Abcam公司,货号ab246514, ab154265);显微镜(日本OLYMBUS公司, BX53型)。

1.3 方法

1.3.1 YTHDF2, UBXN1表达检测:将脑胶质瘤组织和癌旁组织常规固定、包埋、切片,烘片2h后,按照常规免疫组织化学染色方法进行染色。YTHDF2, UBXN1一抗4℃避光过夜,稀释比均为1:500;二抗室温孵育30min;DAB显色,苏木素复染,梯度酒精脱水后树脂封片。镜下观察染色强度和范围,染色强度(0:无颜色,1:浅黄色,2:深黄色)和染色面积(0: $\leq 25\%$, 1:26%~50%, 2: $\geq 51\%$)乘积 < 2 分为阴性, ≥ 2 分为阳性。

1.3.2 术后治疗及随访:脑胶质瘤患者术后均接受放化疗。放疗参考手术前及手术后头颅MRI勾画靶区,根据靶区所在部位确定危及器官,大体肿瘤靶区为MRI T1增强图像显示的术后残留肿瘤和(或)术腔。临床靶区为大体肿瘤靶区外扩2cm,剂量46~50Gy,临床靶区1为大体肿瘤靶区外扩1cm,剂量10~14Gy。放疗结束后4周,辅助替莫唑胺化疗:150~200mg/m²,d1~d5,28天为1周期,共6周期。术后开始随访,随访终点为患者因该病死亡。随访五年,第1~3年每3~6个月电话或门诊随访1次,4~5年每6个月~1年随访1次。从观察起点初次手术当日到终点死亡或观察截止日期所经历的时间为病人的生存时间。随访截止至2023年4月。

1.4 统计学分析 采用SPSS26.0软件分析数据。计数资料以 $n(\%)$ 表示,率比较采用卡方(χ^2)检验。相关性分析采用Spearman秩相关。通过Kaplan-Meier曲线图比较YTHDF2, UBXN1阳性组和阴性组之间的预后差异。多因素COX比例风险模型分析胶质瘤预后影响因素。 $P < 0.05$ 为差异具有统计学意义。

2 结果

2.1 脑胶质瘤和癌旁组织YTHDF2, UBXN1表达 见图1。YTHDF2和UBXN1的棕褐色染色分别定位于胶质瘤和癌旁组织的细胞核。相比于癌旁组织,脑胶质瘤中YTHDF2阳性率较高[65.22%(60/92) vs 15.22%(14/92)],UBXN1的阳性率较低[26.09%(24/92) vs 73.91%(68/92)],差异具有统计学意义($\chi^2=47.831, 42.087$, 均 $P < 0.001$)。脑胶质瘤中YTHDF2与UBXN1表达呈负相关($r=-0.712, P < 0.001$)。

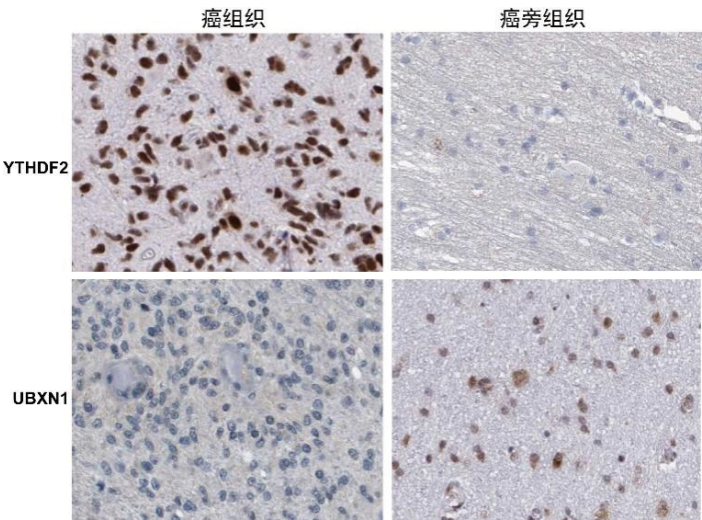


图1 脑胶质瘤中 YTHDF2, UBXN1 表达 (免疫组化, ×200)

2.2 脑胶质瘤中 YTHDF2, UBXN1 表达与临床参数的关系 见表1。相比于肿瘤直径< 3cm, WHO 分级 I ~ II 级, 肿瘤直径 ≥ 3cm 和 WHO 分级 III 级脑胶质瘤组织中 YTHDF2 阳性率较高, 而 UBXN1 阳性率较低, 差异具有统计学意义 (均 $P < 0.05$)。

表1 脑胶质瘤中 YTHDF2, UBXN1 表达与临床参数的关系 [n(%)]

类 别		<i>n</i>	YTHDF2 阳性	χ^2	<i>P</i>	UBXN1 阳性	χ^2	<i>P</i>
年龄 (岁)	≥ 60	42	30 (71.49)	1.314	0.252	10 (23.81)	0.208	0.648
	< 60	50	30 (60.00)			14 (28.00)		
性别	男	51	34 (66.67)	2.605	0.107	13 (25.49)	0.021	0.884
	女	41	26 (48.28)			11 (26.83)		
病理类型	星形胶质细胞瘤	38	25 (65.79)	1.305	0.521	10 (26.32)	0.275	0.871
	少突胶质细胞瘤	34	18 (52.94)			8 (23.53)		
	室管膜瘤	20	17 (85.00)			6 (30.00)		
肿瘤直径 (cm)	≥ 3	53	40 (75.47)	5.795	0.016	8 (15.09)	7.835	0.005
	< 3	39	20 (51.28)			16 (41.03)		
侵犯脑叶数 (个)	< 2	44	26 (59.09)	1.395	0.238	15 (34.09)	2.802	0.094
	≥ 2	48	34 (70.83)			9 (18.75)		
WHO 分级	I ~ II 级	38	19 (50.00)	6.609	0.010	18 (47.37)	15.207	< 0.001
	Ⅲ级	54	41 (65.22)			6 (11.11)		

2.3 YTHDF2, UBXN1 对脑胶质瘤患者生存预后的影响 见图2。随访期间死亡55例, 五年总生存率为40.22% (37/92)。YTHDF2 阳性组和阴性组五年总生存率分别为28.33% (17/60), 62.50% (20/32), YTHDF2 阳性组五年累积生存率低于阴性组, 差异具有统计学意义 (Log-Rank χ^2 =12.870, P =0.000); UBXN1 阳性组和阴性组五年总生存率分别为66.67% (16/24), 30.88% (21/68), UBXN1 阴性组五年累积生存率低于阳性组, 差异具有统计学意义 (Log-Rank χ^2 =7.665, P =0.006)。

2.4 影响脑胶质瘤患者预后的因素 见表2。以患者预后为因变量 (1=死亡, 0=生存)、以年龄 (赋值: ≥ 60岁=1, < 60岁=0)、性别 (赋值: 男=1, 女=0)、侵犯脑叶数 (≥ 2个=1, < 2个=0)、病理类型 (赋值: 星形胶质瘤细胞瘤=1, 0=其它)、肿瘤直径 (≥ 3cm=1, < 3cm=0)、WHO 分级 (赋值: III级=1, I ~ II=0)、YTHDF2 (阳性=1, 阴性=0)、UBXN1 (阳性=1, 阴性=0) 为自变量进行多因素 COX 回归分析, 结果显示 YTHDF2, UBXN1, WHO 分级及肿瘤直径是胶质瘤患者不良

预后的独立因素（均 $P < 0.05$ ）。

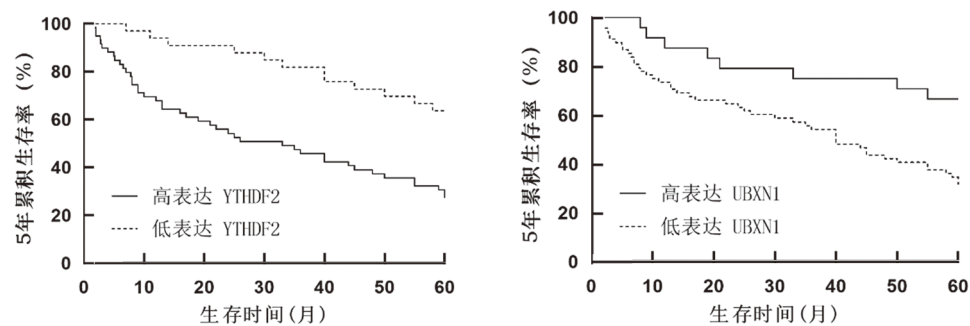


图2 KaplanMeier 曲线分析不同 YTHDF2, UBXN1 表达组胶质瘤患者生存预后差异
多因素 COX 回归模型分析脑胶质瘤患者预后影响因素

因素	β	SE	Wald/ χ^2	P	HR	95%CI
年龄 ≥ 60 岁	0.142	0.115	1.525	0.345	1.153	0.920 ~ 1.444
男性	0.186	0.170	1.197	0.533	1.204	0.863 ~ 1.681
侵犯脑叶数 ≥ 2 个	0.373	0.252	2.191	0.261	1.452	0.867 ~ 2.380
星形胶质细胞瘤	0.246	0.209	1.385	0.344	1.279	0.849 ~ 1.926
WHO 分级Ⅲ级	0.982	0.414	5.476	< 0.001	2.671	1.160 ~ 6.012
肿瘤直径 ≥ 3 cm	0.479	0.230	4.363	0.001	1.628	1.017 ~ 2.592
YTHDF2 阳性	0.910	0.268	9.553	< 0.001	2.427	1.426 ~ 4.569
UBXN1 阴性	0.569	0.221	6.867	< 0.001	1.740	1.121 ~ 2.568

3 讨论

脑胶质瘤是人类常见恶性肿瘤,发病率约 6.4/10 万^[8]。脑胶质瘤恶性程度高,具有高度侵袭性和转移性,细胞呈弥漫性浸润,对现有治疗存在普遍的耐药性,即使经积极手术、放化疗及免疫等综合治疗,患者远期生存率仍然较低,预后较差^[9]。脑胶质瘤的发病机制尚不清楚,与遗传因素、环境因素等有关。研究脑胶质瘤发生发展中的生物学机制,寻找协助预后预测的生物标志物,对于推进脑胶质瘤的精准治疗意义重大。

m6A 修饰是真核生物中 RNA 最丰富且高度保守的修饰方式,由 m6A 阅读者、书写者及擦除者三部分组成,维持 mRNA 成熟、稳定性、剪接及翻译等生物功能。YTHDF2 是 m6A 修饰的阅读者,能够与 m6A 标记的 mRNA 高亲和力结合,参与调节细胞分化、细胞自我更新及维持干细胞状态等过程,与肿瘤的发生发展密切相关^[10]。本研究中,脑胶质瘤组织中 YTHDF2 表达升高,这与既往学者在癌症基因组图谱数据库中的分析结果一致^[11],但该研究仅在转录水平分析 YTHDF2 mRNA 表达,未能在蛋白水平进一步验证。本研究进一步证实脑胶质瘤中 YTHDF2 蛋白表达升高,提示 YTHDF2 参与脑胶质瘤的发生。YTHDF2 的表达升高与蛋白稳定性增加有关。研究表明,胶质母细胞瘤中表皮生长因子受体能够组成型激活细胞外信号调节激酶途

径,诱导 YTHDF2 蛋白丝氨酸 39 和苏氨酸 381 位点的磷酸化,增加 YTHDF2 蛋白的稳定性和蛋白表达,而 YTHDF2 能够促进肝 X 受体 mRNA 的 m6A 修饰,促进癌细胞的增殖、侵袭^[12]。本研究发现,YTHDF2 的表达与脑胶质瘤直径及 WHO 分级有关,提示 YTHDF2 促进脑胶质瘤的肿瘤进展。研究发现,YTHDF2 的表达上调能够稳定胶质瘤细胞中的 MYC mRNA 和血管内皮生长因子 A mRNA,促进癌细胞的恶性增殖及肿瘤血行转移^[11]。另有学者发现,YTHDF2 能够促进肿瘤微环境中巨噬细胞重新编程为 M2 型肿瘤相关巨噬细胞,抑制 CD8⁺T 细胞介导的抗肿瘤免疫,导致肿瘤免疫逃逸,而利用小干扰 RNA 选择性靶向抑制 YTHDF2 的表达后,巨噬细胞重编程为抗肿瘤 M1 表型,显著增强 CD8⁺T 细胞的肿瘤杀伤能力,同时增强免疫检查点抑制剂的疗效^[13]。本研究中,YTHDF2 阳性脑胶质瘤患者预后较差,提示 YTHDF2 是评估脑胶质瘤预后的标志物。分析原因,YTHDF2 的表达能够增加肿瘤细胞对放化疗及靶向治疗的耐药性,导致患者不良预后^[14]。有学者通过抑制 YTHDF2 的表达,抑制下游核因子 KB 信号通路,减少免疫抑制性骨髓源性抑制细胞的分化和浸润,增强肿瘤细胞对放射治疗的敏感性^[15]。

UBXN1 编码基因位于 11q12.3,其羧基端具有 UBX 结构域,与 E3 泛素连接酶结合,参与泛

素依赖性蛋白质降解、囊泡融合和细胞周期控制等多种细胞过程,在肿瘤、自身免疫疾病及炎症等疾病中发挥重要的调节作用^[5]。本研究中,脑胶质瘤组织中UBXN1表达降低,这与既往学者在脑胶质瘤细胞系U87-MG, HT29中发现的UBXN1表达下调的结果一致^[16],提示UBXN1与脑胶质瘤的发生有关。UBXN1表达下调与表观遗传学调控失常有关。有学者报道,胶质母细胞瘤中链非编码RNA PRADX的表达升高,其可通过5'端序列与果蝇Zeste基因增强子2蛋白结合形成复合物,促进癌细胞中组蛋白H3赖氨酸27三甲基化,抑制UBXN1基因的表达,导致UBXN1的下游靶点I κ B α 降解减少,核因子 κ B通路过度激活,促进癌细胞的过度增殖^[16]。本研究中,UBXN1的表达与脑胶质瘤直径及WHO分级有关,提示UBXN1的表达下调促进脑胶质瘤的进展。笔者分析,脑胶质瘤中UBXN1作为一种抑癌因子,参与抑制肿瘤增殖和转移。研究表明,UBXN1能够与环状RNA MRE11A结合,诱导共转录失调毛细血管扩张突变激酶的激活,启动p53/p21信号通路,阻滞癌细胞周期的进行^[17]。另有学者发现,脑胶质瘤细胞中链非编码RNA NEAT1通过抑制UBXN1的表达,增强程序性死亡因子配体1的表达,抑制CD8⁺T细胞的浸润和癌细胞杀伤毒性,促进肿瘤细胞的免疫逃避^[18]。本研究中,UBXN1阴性表达是影响脑胶质瘤患者不良预后的独立因素,表明UBXN1是评估脑胶质瘤患者预后的标志物。分析其机制,UBXN1的下调促进受体相互作用蛋白K63的泛素化,诱导I κ B α 的分解,激活表皮生长因子的表达,增强癌细胞的抗凋亡能力,降低癌细胞对放疗治疗的敏感性,导致患者不良预后^[19]。有学者利用CRISPR/Cas9敲除表皮生长因子受体外显子17上的vIII基因,UBXN1的表达上调,癌细胞的增殖和侵袭能力明显受到抑制,提示以UBXN1为靶点的治疗可能是携带表皮生长因子受体基因突变患者的有前途的治疗策略^[20]。本研究中,YTHDF2与UBXN1表达呈负相关,表明两者在脑胶质瘤中存在相互作用。研究报道,YTHDF2通过甲基转移酶3介导的m6A修饰促进UBXN1 mRNA的降解,促进下游核因子 κ B的激活,诱导胶质瘤的增殖和转移,而UBXN1过表达减弱了YTHDF2过表达对胶质瘤细胞的致癌作用^[21]。

综上所述,脑胶质瘤中YTHDF2升高,UBXN1降低,两者与WHO分级及肿瘤直径有关,两者均促进脑胶质瘤的肿瘤进展。YTHDF2,UBXN1是影响胶质瘤患者预后的独立因素,临床上可根据YTHDF2,UBXN1的表达,结合传统的WHO分级

和肿瘤直径等临床病理特征,对脑胶质瘤患者的预后进行综合评估,指导临床治疗。本研究未能对脑胶质瘤中YTHDF2,UBXN1表达的作用机制进行研究,两者能否成为新的脑胶质瘤治疗靶点,值得今后进行深入研究。

参考文献:

- [1] SCHAFF L R, MELLINGHOFF I K. Glioblastoma and other primary brain malignancies in adults: a review[J]. Journal of the American Medical Association, 2023, 329(7): 574-587.
- [2] CAI Jiayang, HU Yuanyuan, YE Zhang, et al. Immunogenic cell death-related risk signature predicts prognosis and characterizes the tumour microenvironment in lower-grade glioma[J]. Frontiers in Immunology, 2022, 13: 1011757.
- [3] YU Jie, CHAI Peiwei, XIE Minyue, et al. Histone lactylation drives oncogenesis by facilitating m(6) A reader protein YTHDF2 expression in ocular melanoma[J]. Genome Biology, 2021, 22(1): 85.
- [4] LI Jiangfeng, XIE Haiyun, YING Yufan, et al. YTHDF2 mediates the mRNA degradation of the tumor suppressors to induce AKT phosphorylation in N6-methyladenosine-dependent way in prostate cancer[J]. Molecular Cancer, 2020, 19(1): 152.
- [5] MENGUS C, NEUTZNER M, BENTO A C P F, et al. VCP/p97 cofactor UBXN1/SAKS1 regulates mitophagy by modulating MFN2 removal from mitochondria [J]. Autophagy, 2022, 18(1): 171-190.
- [6] YIN Xiu, LIU Qingbin, LIU Fen, et al. Emerging roles of non-proteolytic ubiquitination in tumorigenesis [J]. Frontiers in Cell and Developmental Biology, 2022, 10: 944460.
- [7] OH J J, HO J N, BYUN S S. ARRDC4 and UBXN1: novel target genes correlated with prostate cancer gleason score[J]. Cancers, 2021, 13(20): 5209.
- [8] MO Zongchao, XIN Junyi, CHAI Ruichao, et al. Epidemiological characteristics and genetic alterations in adult diffuse glioma in East Asian populations[J]. Cancer biology & Medicine, 2022, 19(10): 1440-1459.
- [9] 刁迅, 范绮雨, 耿良栋, 等. 基于生物信息学分析双硫死亡相关基因PDLIM1 mRNA在多种肿瘤中的表达及临床应用价值[J]. 现代检验医学杂志, 2024, 39(1): 36-42, 54.
DIAO Xun, FAN Qiyu, GENG Liangdong, et al. Analysis of expression in disulfidptosis-related gene PDLIM1 mRNA in various tumors and its clinical application value based on bioinformatics[J]. Journal of Modern Laboratory Medicine, 2024, 39(1): 36-42, 54.
- [10] WANG Liangliang, DOU Xiaoyang, CHEN Shijie, et al. YTHDF2 inhibition potentiates radiotherapy antitumor efficacy [J]. Cancer Cell, 2023, 41(7): 1294-1308, e8.
- [11] DIXIT D, PRAGER B C, GIMPLE R C, et al. The RNA m6A reader YTHDF2 maintains oncogene expression and is a targetable dependency in glioblastoma stem cells[J]. Cancer Discovery, 2021, 11(2): 480-499.
- [12] FANG Rungping, CHEN Xin, ZHANG Sicong, et al. EGFR/

(下转第210页)

- WANG Zhichao, WU Qi, FENG Fanchao, et al. Isolation and purification of adult mouse lung fibroblasts by efficient and modified tissue method[J]. Chinese Archives of Traditional Chinese Medicine, 2018, 36(12): 2842-2844, F0002-F0003.
- [6] ABADE DOS SANTOS FA, CARVALHO CL, ALMEIDA I, et al. Simple method for establishing primary leporidae skin fibroblast cultures[J]. Cells, 2021, 10(8): 2100.
- [7] TAJIMA K, OKADA M, KUDO R, et al. Primary cell culture of canine corneal endothelial cells [J]. Veterinary Ophthalmology, 2021, 24(5): 447-454.
- [8] CAVAGNERO K J, GALLO R L. Essential immune functions of fibroblasts in innate host defense [J]. Frontiers in Immunology, 2022, 13: 1058862.
- [9] GROUT J A, SIRVEN P, LEADER A M, et al. Spatial positioning and matrix programs of cancer-associated fibroblasts promote T-cell exclusion in human lung tumors[J]. Cancer Discovery, 2022, 12(11): 2606-2625.
- [10] GONG Zheng, LI Qing, SHI Jiayuan, et al. Lung fibroblasts facilitate pre-metastatic niche formation by remodeling the local immune microenvironment[J]. Immunity, 2022, 55(8): 1483-1500, e9.
- [11] PHOGAT S, THIAM F, AL YAZEEDI S, et al. 3D in vitro hydrogel models to study the human lung extracellular matrix and fibroblast function[J]. Respiratory Research, 2023, 24(1): 242.
- [12] CHARNI-NATAN M, GOLDSTEIN I. Protocol for primary mouse hepatocyte isolation [J]. STAR Protocols, 2020, 1(2): 100086.
- [13] 刘先宁, 汪耀, 朱秀萍, 等. 人角膜基质间充质干细胞的分离培养及表型鉴定 [J]. 现代检验医学杂志, 2019, 34(4): 28-30, 34.
- LIU Xianning, WANG Yao, ZHU Xiuping, et al. Isolation, culture and phenotype identification of human corneal stromal mesenchymal stem cells[J]. Journal of Modern Laboratory Medicine, 2019, 34(4): 28-30, 34.
- [14] PATEL B B, CLARK K L, KOZIK E M, et al. Isolation and culture of primary embryonic zebrafish neural tissue [J]. Journal of Neuroscience Methods, 2019, 328: 108419.
- [15] VALYI-NAGY K, BETSOU F, SUSMA A, et al. Optimization of viable glioblastoma cryopreservation for establishment of primary tumor cell cultures[J]. Biopreservation and Biobanking, 2021, 19(1): 60-66.
- [16] EHLEN L, ARNDT J, TREUE D, et al. Novel methods for in vitro modeling of pancreatic cancer reveal important aspects for successful primary cell culture[J]. BMC Cancer, 2020, 20(1): 417.
- [17] 刘姿麟, 林慕之, 况春燕, 等. 大鼠主动脉血管平滑肌细胞原代培养与鉴定 [J]. 贵州医科大学学报, 2017, 42(2): 125-129.
- LIU Zilin, LIN Muzhi, KUANG Chunyan, et al. Culture and identification of primary generation of vascular smooth muscle cell of rat[J]. Journal of Guizhou Medical University, 2017, 42(2): 125-129.
- [18] 钱凯, 唐琳俊, 王希, 等. 新生大鼠原代小胶质细胞分离培养方法的改良 [J]. 临床神经外科杂志, 2019, 16(1): 1-5.
- QIAN Kai, TANG Linjun, WANG Xi, et al. Modified method for cultivating primary microglia of neonatal rat[J]. Journal of Clinical Neurosurgery, 2019, 16(1): 1-5.
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- (上接第134页)
- SRC/ERK-stabilized YTHDF2 promotes cholesterol dysregulation and invasive growth of glioblastoma[J]. Nature Communications, 2021, 12(1): 177.
- [13] MA Shoubao, SUN Baofa, DUAN Songqi, et al. YTHDF2 orchestrates tumor-associated macrophage reprogramming and controls antitumor immunity through CD8⁺ T cells[J]. Nature Immunology, 2023, 24(2): 255-266.
- [14] LIAO Yuning, LIU Yuan, YU Cuifu, et al. HSP90 β impedes STUB1-induced ubiquitination of YTHDF2 to drive sorafenib resistance in hepatocellular carcinoma[J]. Advanced Science Weinheim Baden Wurttemberg Germany, 2023, 10(27): 2302-23025.
- [15] WANG Liangliang, DOU Xiaoyang, CHEN Shijie, et al. YTHDF2 inhibition potentiates radiotherapy antitumor efficacy [J]. Cancer Cell, 2023, 41(7): 1294-1308, e8.
- [16] LI Yansheng, LIU Xing, CUI Xiaoteng, et al. LncRNA PRADX-mediated recruitment of PRC2/DDX5 complex suppresses UBXXN1 expression and activates NF- κ B activity, promoting tumorigenesis[J]. Theranostics, 2021, 11(9): 4516-4530.
- [17] LIU Junliang, ZHANG Jinling, ZHANG Guowei, et al. CircMRE11A_013 binds to UBXXN1 and integrates ATM activation enhancing lens epithelial cells senescence in age-related cataract[J]. Aging (Albany NY), 2021, 13(4): 5383-5402.
- [18] YI Kaikai, CUI Xiaoteng, LIU Xing, et al. PTRF/cavin-1 as a novel RNA-binding protein expedites the NF- κ B/PD-L1 axis by stabilizing lncRNA NEAT1 [J]. Frontiers in Immunology, 2021, 12: 802795.
- [19] DAN Wenran, ZHONG Liang, ZHANG Zhonghui, et al. RIP1-dependent apoptosis and differentiation regulated by Skp2 and Akt/GSK3 β in acute myeloid leukemia[J]. International Journal of Medical Sciences, 2022, 19(3): 525-536.
- [20] YANG Enyu, FAN Xiaowei, YE Haihan, et al. Exploring the role of ubiquitin regulatory X domain family proteins in cancers: bioinformatics insights, mechanisms, and implications for therapy[J]. Journal of Translational Medicine, 2024, 22(1): 157.
- [21] CHAI Ruichao, CHANG Yuzhou, CHANG Xin, et al. YTHDF2 facilitates UBXXN1 mRNA decay by recognizing METTL3-mediated m6A modification to activate NF- κ B and promote the malignant progression of glioma[J]. Journal of Hematology & Oncology, 2021, 14(1): 109.
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