

LASP1 在鼻咽癌组织中的表达及其临床预后价值分析

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摘 要: [目的] 探讨 LASP1 在鼻咽癌组织中的表达与预后的关系, 及其在鼻咽癌中的功能。 [方法] 免疫组化法检测 79 例鼻咽癌患者组织标本中 LASP1 蛋白的表达。Western Blot 和 Real-time PCR 检测鼻咽癌细胞株中 LASP1 表达。Transwell 小室实验明确体外 LASP1 对细胞迁移和侵袭能力的影响。Kaplan-Meier 法分析 LASP1 表达与患者预后的关系, Cox 比例风险回归模型分析 LASP1 表达在鼻咽癌患者预后预测中的价值。 [结果] LASP1 在鼻咽癌组织 (0.087 ± 0.103) 表达显著高于癌旁组织 (0.016 ± 0.010) ($t=2.154, P=0.034$)。LASP1 在 N_{2-3} 期 ($\chi^2=38.406, P<0.001$) 与 IV 期 ($\chi^2=4.595, P=0.043$) 患者表达较 N_{0-1} 和 II~III 期患者更高。LASP1 高表达与低表达两组患者总生存 (overall survival, OS)、无远处转移生存 (distant metastasis free survival, DMFS) 和无局部复发生存 (relapse free survival, RFS) 分别为 (114.5 ± 8.5) 个月 vs (137.5 ± 4.6) 个月 ($P=0.038$)、(112.3 ± 9.1) 个月 vs (140.3 ± 3.8) 个月 ($P=0.009$) 和 (108.6 ± 9.4) 个月 vs (134.6 ± 5.3) 个月 ($P=0.029$)。LASP1 高表达 ($HR=4.437, 95\%CI: 1.148 \sim 17.415, P=0.031$) 和 TNM 分期 ($HR=5.512, 95\%CI: 1.075 \sim 28.254, P=0.041$) 是患者生存的独立预测因素。LASP1 在鼻咽癌细胞株中表达 (1.47 ± 0.35) 较正常鼻咽上皮细胞株 (0.90 ± 0.11) 也显著升高 ($t=4.488, P<0.001$)。过表达 LASP1 的鼻咽癌细胞株与对照组相比, Transwell 小室细胞侵袭 [(238.7 ± 36.2) vs (48.7 ± 11.6)]、迁移 [(571.0 ± 15.7) vs (91.6 ± 20.3)] 能力显著增强 ($P<0.01$)。采用特异性 shRNA 敲低 LASP1 表达, 鼻咽癌细胞体外侵袭 [(168.7 ± 14.6) vs (64.3 ± 7.4)] 和迁移 [(205.0 ± 9.8) vs (79.0 ± 10.5)] 能力受到抑制 ($P<0.01$)。 [结论] LASP1 在鼻咽癌组织和细胞中过表达, 与鼻咽癌患者分期相关, 且 LASP1 高表达是患者预后不良因素。体外功能实验表明 LASP1 发挥促进肿瘤侵袭和迁移功能。提示 LASP1 在鼻咽癌进展中发挥重要作用, 可作为鼻咽癌诊治新的分子靶点。

关键词: 鼻咽肿瘤; LASP1; 免疫组化; 预后; 总生存

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Expression and Prognostic Value of LASP1 in Nasopharyngeal Carcinoma

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Abstract: [Purpose] To explore the expression and prognostic value of LASP1 in nasopharyngeal carcinoma (NPC), and to identify the function of LASP1 in NPC. [Methods] Immunohistochemistry was adopted to determine LASP1 expression in 79 primary tumor samples and adjacent tissues from NPC patients. Western Blot and real time PCR were used to determine LASP1 expression in NPC cell lines. Transwell migration and invasion assay were used to determine the effect of LASP1 on cell migration and invasion *in vitro*. Kaplan-Meier plots were performed to investigate the prognostic relevance of LASP1 in univariate analysis. Multivariate analysis was performed by Cox proportional hazards models. [Results] LASP1 overexpressed in tumor tissues (0.087 ± 0.103) compared with adjacent tissues (0.016 ± 0.010) ($t=2.154, P=0.034$). The high expression of LASP1 was more frequent in patients with N_{2-3} ($\chi^2=38.406, P<0.001$) and stage IV ($\chi^2=4.595, P=0.043$) disease compared with N_{0-1} and stage II~III disease. The overall survival (OS), distant metastasis free survival (DMFS) and relapse free survival (RFS) of patients with high and low expression of LASP1 were (114.5 ± 8.5) months vs (137.5 ± 4.6) months ($P=0.038$), (112.3 ± 9.1) months vs (140.3 ± 3.8) months ($P=0.009$), and (108.6 ± 9.4) months vs (134.6 ± 5.3) months ($P=0.029$). High expression of LASP1 ($HR=4.437, 95\%CI: 1.148 \sim 17.415, P=0.031$) and TNM staging ($HR=5.512, 95\%CI: 1.075 \sim 28.254$,

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$P=0.041$) were independent prognostic factor for OS in NPC patients. LASP1 was significantly up-regulated in NPC cell lines (1.47 ± 0.35) in comparison with immortalized nasopharyngeal epithelial cells (0.90 ± 0.11) ($t=4.488, P<0.001$). In comparison with control group, NPC cells with LASP1 over-expressed showed increased invasion (238.7 ± 36.2 vs 48.7 ± 11.6) and migration (571.0 ± 15.7 vs 91.6 ± 20.3) ($P<0.01$) potency. Moreover, LASP1 knockdown assay with specific sh-RNA significantly inhibited its invasion (168.7 ± 14.6 vs 64.3 ± 7.4) and migration (205.0 ± 9.8 vs 79.0 ± 10.5) *in vitro* ($P<0.01$). [Conclusion] LASP1 overexpression is observed in NPC cell lines and primary tumor of NPC patients, which is correlated with advanced disease and inferior survival. *In vitro* functional assays show that LASP1 promote tumor migration and invasion. It suggests that LASP1 plays crucial role in tumor progression and maybe serve as a therapeutic target in NPC.

Key words: nasopharyngeal neoplasms; LASP1; immunohistochemistry; prognosis; overall survival

鼻咽癌是起源于鼻咽黏膜的恶性肿瘤,全球有40%鼻咽癌发病于中国^[1]。现有治疗模式下,鼻咽癌局部控制率已达到93%,复发或转移已成为患者死亡的主要原因^[2-6]。因此,明确鼻咽癌患者预后相关分子机制,有助于为临床治疗提供新的分子标志和治疗靶点。

LASP1 (LIM and SH3 protein 1)最初从乳腺癌转移性淋巴结(metastatic axillary lymph nodes, MLN) cDNA 文库中鉴定得到,又名 MLN50^[7],在肌动蛋白(actin)聚集处起到结构支架蛋白的作用;还能转位至细胞核发挥细胞核转导分子的功能^[8,9]。LASP1在多种肿瘤组织高表达,参与肿瘤迁移、粘附、增殖等过程^[10-14]。我们的前期研究发现, microRNA(miR)-203在鼻咽癌中通过抑制 LASP1 发挥抑制肿瘤生长转移的功能^[15]。然而, LASP1在鼻咽癌预后预测中的价值鲜有报道。

本文通过免疫组化和 Real-time PCR 等技术检测 LASP1 在鼻咽癌组织和细胞中的表达,并分析 LASP1 表达状态与患者临床参数的关系,进一步观察 LASP1 上调和下调对鼻咽癌细胞株体外侵袭、迁移能力的影响。本文旨在明确 LASP1 在鼻咽癌中的功能,为鼻咽癌临床诊断和治疗提供新的分子标志物和靶点。

1 资料与方法

1.1 临床资料和细胞株来源

本研究选取江苏省肿瘤医院 2005 年 10 月至 2010 年 11 月病理证实为鼻咽癌的石蜡组织标本。纳入标准:①既往未接受放化疗;②年龄大于 18 周

岁;③没有其他恶性肿瘤病史;④有完整随访资料。共筛选出鼻咽癌石蜡标本 79 例。所有患者标本均经过 HE 染色检查和病理科医师阅片确诊;TNM 分期采用 AJCC/UICC 第 8 版分期标准。随访时间从开始接受治疗的第 1 天算起,至患者死亡或最后 1 次复查。鼻咽癌细胞株 HNE1、SUNE1、CNE2、CNE1 和 HONE1,以及人鼻咽正常上皮细胞株 NP-69 和 N2-TERT 由江苏省肿瘤医院放疗科实验室长期保存。本研究经过江苏省肿瘤医院伦理委员会的批准。

1.2 免疫组化

将鼻咽癌蜡块切成 $2\mu\text{m}$ 薄片置于载玻片上。脱蜡及脱水后采用柠檬酸钠缓冲溶液进行抗原修复, LASP1 一抗(购于 Proteintech 公司, 10515-1-AP) 4°C 孵育过夜;0.05% PBS Triton 清洗后,二抗室温孵育 1h;0.05% PBS Triton 清洗后,含有 DAPI 的封片剂染色并封片。 -20°C 闭光保存,激光共聚焦显微镜观察。每张切片随机取 3 个视野,采用目镜 20 倍、物镜 10 倍放大视野,利用 ImagePro Plus 软件对免疫组化结果进行定量分析。简单过程如下:选取图片上目标分析区域,测量该区域的积分光密度 (integrated option density, IOD)。选择并测量有效统计区域的面积,计算选择区域内的光密度平均值 IOD/area (mean density, MD)。用于免疫组化染色的 ABC 染色试剂盒以及 DAB 显色试剂盒均购于 Vector Laboration 公司。

1.3 Western Blot 实验

细胞在 P100 培养皿中培养至对数生长期约为 80%~90%融合度,收提取蛋白。使用 Bio Rad Protein Assay Kit 试剂盒测算蛋白样品浓度。采用 Bio-Rad 电泳槽进行电泳,并将蛋白转到 PVDF 膜上。放

入 LASP1 一抗(1:1000)孵育过夜后,放入对应的二抗中,室温摇床上摇晃孵育 1h,按超敏发光液试剂盒说明书操作,进行显影和定影。胶片扫描存档。

1.4 Real-time PCR 实验

提取细胞株总 RNA 后,采用通用 M-MLV 逆转录酶(Promega,M1705)进行转录。采用 SYBR Green qPCR SuperMix-UDG(Invitrogen,11733)按说明书提示在 ABI 7300 PCR 仪器平台进行半定量 qPCR 检测,采用 *GAPDH* 为内参。LASP1 相对表达值计算按文献[15]中描述进行。

1.5 Transwell 小室侵袭和迁移实验

细胞侵袭和迁移实验采用 Transwell 小室(Corning,3422)进行。将 SUNE1 细胞收集离心后,混悬于无血清培养基中,以 5×10^4 密度种到 Transwell 小室中。小室放入加有 10%胎牛血清的培养基中培养 24h 后取出,固定后镜下观察计数。Transwell 侵袭实验使用铺有基质胶(BD Biosciences,356213)的小室进行实验。

1.6 统计学处理

所有统计学分析均采用 SPSS20.0 软件。所有变量以均数 $\pm$ 标准差表示。数据组间比较采用配对资料 *t* 检验,LASP1 表达与鼻咽癌患者临床病理特征关系分析采用卡方检验,采用 Kaplan-Meier 法进行生存分析并绘制生存曲线,Log-rank 检验明确 LASP1 高表达和低表达组生存率差异是否具有统计学意义。多因素预后分析采用 Cox 比例风险回归模型。 $P < 0.05$ 为差异有统计学意义。

2 结果

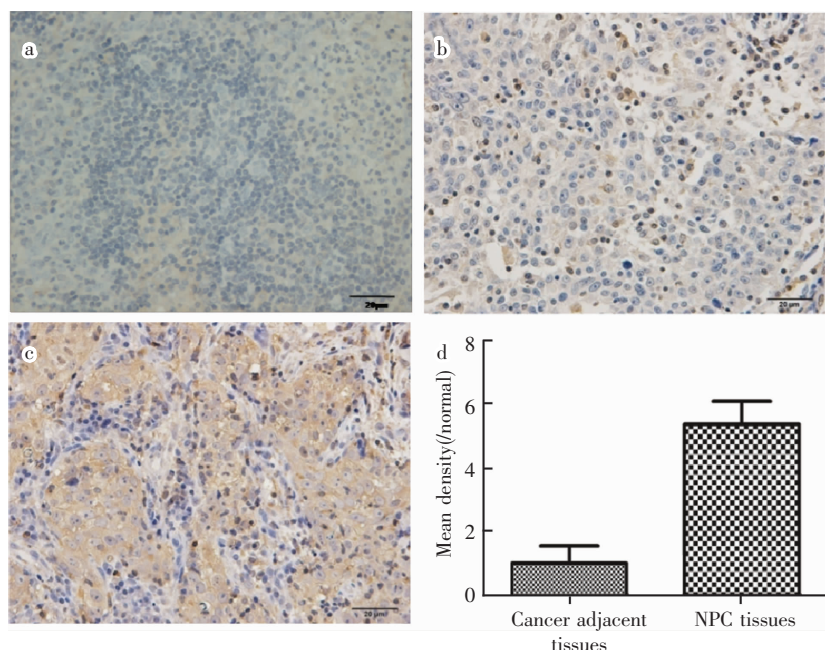
2.1 LASP1 在鼻咽癌组织中的表达

本研究回顾性纳入鼻咽癌患者共 79 例,患者中位年龄 48.7 岁(17~74 岁),男性 58 例,女性 21 例。其中 AJCC/UICC TNM 分期 II~III 期患者

39 例,IV 期患者 40 例。在所有 79 例患者中,采用 3DRT 技术放疗共 19 例,采用 IMRT 放疗技术 60 例。放疗平均剂量为 (70 ± 3.55) Gy。放疗处方剂量情况:原发灶(GTVnx):66~75 Gy/31~35 次;淋巴结转移灶(GTVnd):65~75 Gy/32~35 次;高危淋巴结引流区(CTV1):56~60 Gy/30 次;低危淋巴结引流区(CTV2):50 Gy/30 次。本组患者中,35 例(44.3%)患者接受诱导化疗,69 例(87.3%)患者接受了同步化疗,62 例(78.5%)患者接受了辅助化疗。免疫组化检测 79 例鼻咽癌组织和 10 例癌旁组织中 LASP1 蛋白表达水平,LASP1 主要表达在细胞浆中,在鼻咽癌组织中较癌旁组织表达显著升高(Figure 1a、b、c)。LASP1 表达定量分析发现,鼻咽癌组织中 LASP1 表达 MD 为 (0.087 ± 0.103) ,显著高于癌旁组织 (0.016 ± 0.010) ($t = 2.154, P = 0.034$) (Figure 1d)。

2.2 LASP1 表达与鼻咽癌患者临床病理特征的关系

以 LASP1 免疫组化定量分析结果 MD=0.046 为基准,将鼻咽癌患者分为 LASP1 高表达组(38 例)和低表达组(41 例)。结果显示, N_{2-3} 期患者 LASP1 高表达率显著高于 N_{0-1} 期鼻咽癌患者 ($\chi^2 = 38.406, P < 0.001$),TNM 分期 IV 期患者较 II 和 III 期患者 LASP1 表达率



Note: a: LASP1 low expression in cancer adjacent tissues; b: LASP1 low expression in NPC tissues; c: LASP1 high expression in NPC tissues; d: Expression of LASP1 was significantly higher in NPC than that in normal tissues ($P = 0.034$).

Figure 1 The expression of LASP1 in nasopharyngeal cancer(NPC) and cancer adjacent tissues

Table 1 Relationship of LASP1 expression with clinical parameters

Variables	N	LASP1 low expression	LASP1 high expression	χ^2	P
Age(years)					
>48	34	18	16	0.026	1.000
≤48	45	23	22		
Gender					
Male	58	32	26	0.937	0.446
Female	21	9	12		
KPS					
>80	14	7	7	0.025	1.000
≤80	65	34	31		
T stage					
1~2	35	20	15	0.692	0.498
3~4	44	21	23		
N stage					
0~1	39	34	5	38.406	<0.001
2~3	40	7	33		
TNM stage					
II ~ III	39	25	14	4.595	0.043
IV	40	16	24		

有显著统计学差异($\chi^2=4.595$, $P=0.043$)(Table 1)。

2.3 LASP1 表达与鼻咽癌患者生存的关系

79 例患者的中位随访时间为 125.8 个月 (1.3~145.7 个月), 5 年生存率 84.7%。Kaplan-Meier 生存分析和 Log-rank 检验结果提示, LASP1 高表达组患者总生存 (overall survival, OS) (114.5 ± 8.5 个月 vs 137.5 ± 4.6 个月, $P=0.038$), 无远处转移生存 (distant metastasis free survival, DMFS) (112.3 ± 9.1 个月 vs 140.3 ± 3.8 个月, $P=0.009$) 和无局部复发生存 (relapse free survival, RFS) (108.6 ± 9.4 个月 vs 134.6 ± 5.3 个月, $P=0.029$) 均显著高于低表达组 (Figure 2)。Cox 比例风险模型分析结果提示, LASP1 高表达 (HR=

4.437, 95%CI: 1.148~17.415, $P=0.031$) 和 TNM 分期 (HR=5.512, 95%CI: 1.075~28.254, $P=0.041$) 是鼻咽癌患者独立预后因素 (Table 2)。

2.4 LASP1 在鼻咽癌细胞株中的表达情况

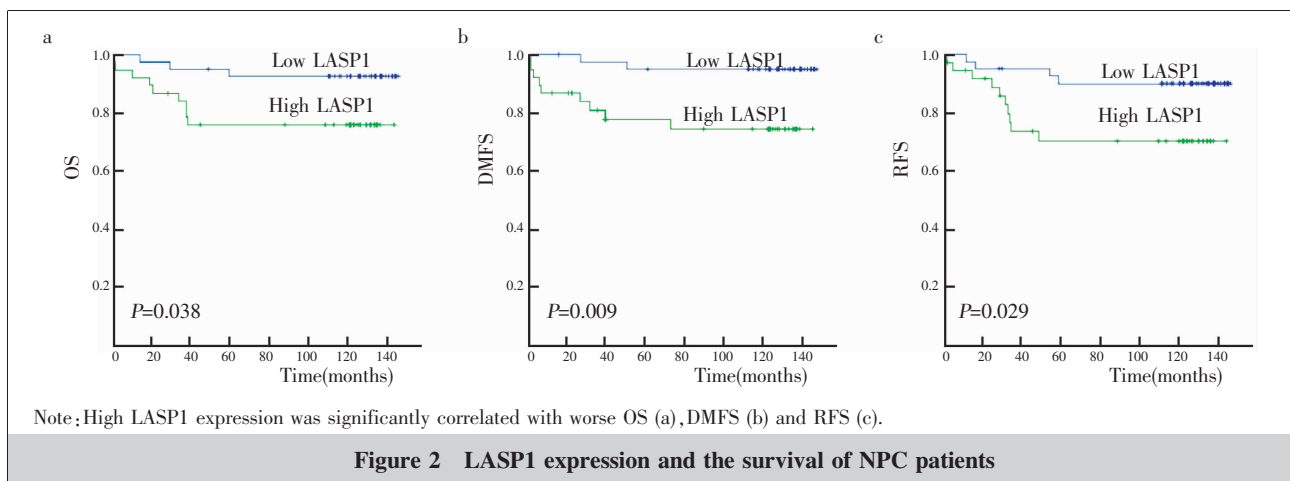
Real time PCR 和 Western Blot 检测 LASP1 在鼻咽癌细胞株以及正常鼻咽永生上皮细胞株 NP-69 和 N2-TERT 中表达。结果显示, LASP1 蛋白水平在鼻咽癌细胞株中明显升高 (Figure 3a), mRNA 水平 ($2^{-\Delta\Delta CT}=1.47 \pm 0.35$) 也显著高于永生鼻咽上皮细胞株 ($2^{-\Delta\Delta CT}=0.90 \pm 0.11$) ($t=4.488$, $P<0.001$) (Figure 3b)。

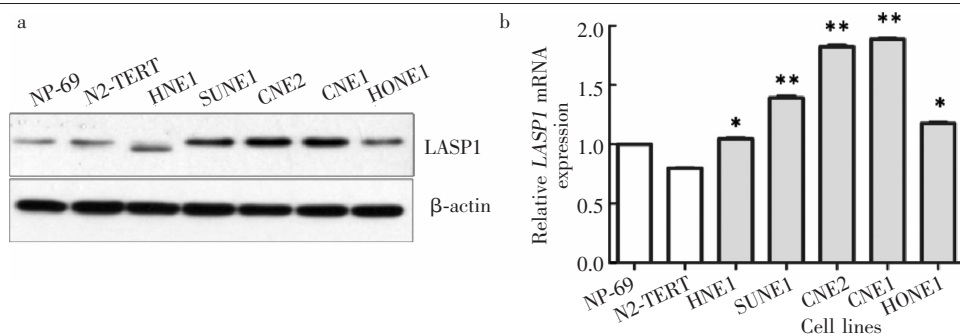
2.5 LASP1 在体外对鼻咽癌细胞侵袭、迁移过程的影响

采用瞬时转染方式在鼻咽癌细胞株中过表达 LASP1 (Figure 4a)。Transwell 侵袭和迁移实验结果表明, 过表达 LASP1 可显著促进 SUNE1 细胞迁移和侵袭 [(571.0 ± 15.7) vs (91.6 ± 20.3) ; (238.7 ± 36.2) vs (48.7 ± 11.6)] ($P<0.001$) (Figure 4b~4d)。设计特异性针对 LASP1 的 shRNA 敲低其表达 (Figure 5a), Transwell 侵袭和迁移实验结果表明, LASP1 敲低后 SUNE1 细胞迁移和侵袭受到明显抑制 [(205.0 ± 9.8) vs (79.0 ± 10.5) ; (168.7 ± 14.6) vs (64.3 ± 7.4)] ($P<0.001$) (Figure 5b~5d)。

Table 2 Multivariate analysis of OS in NPC patients

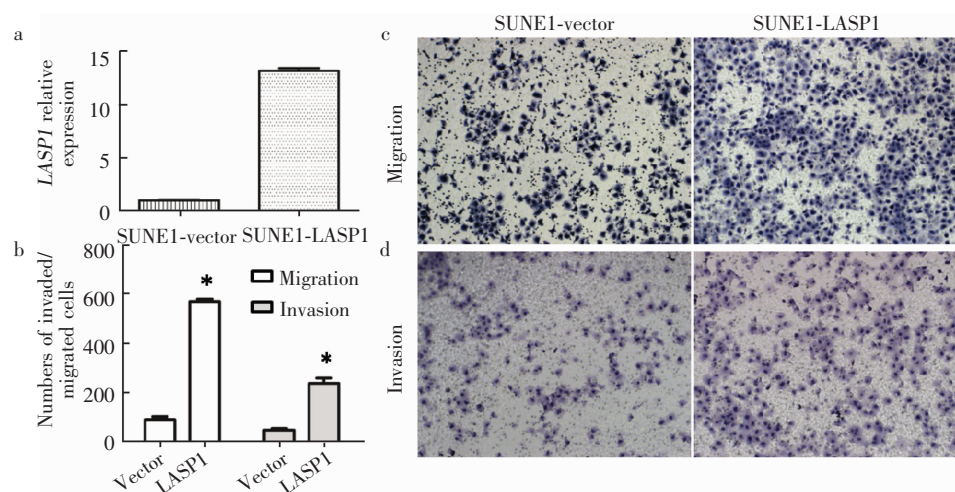
Variables	HR(95%CI)	P
Gender	0.186 (0.024~1.460)	0.110
Age	1.836 (0.535~6.304)	0.334
KPS	3.361 (0.445~3.291)	0.229
Stage	5.512 (1.075~28.254)	0.041
LASP1	4.437 (1.148~17.415)	0.031





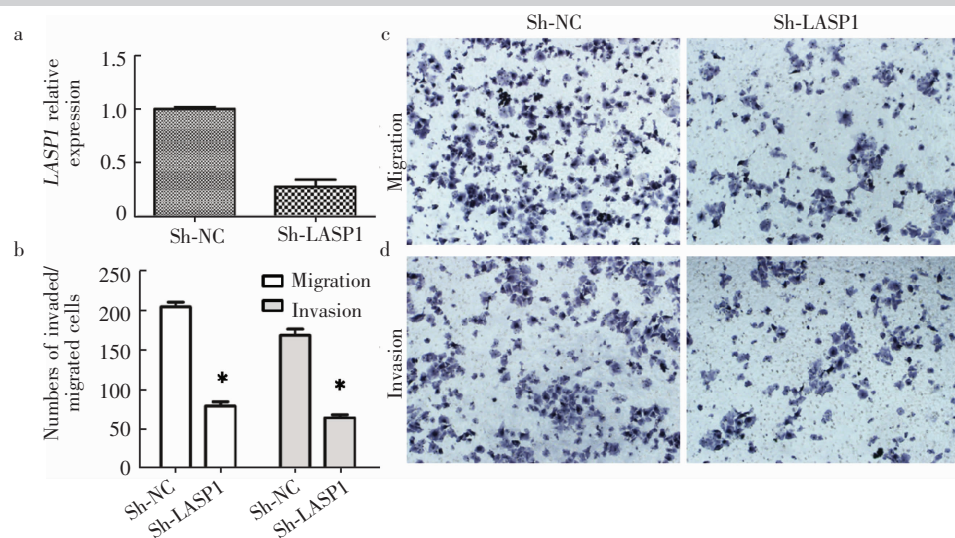
Notes: a; LASP1 protein levels in 5 NPC and 2 normal nasopharyngeal cell lines; b; LASP1 mRNA level was much higher in NPC cell lines. *: $P < 0.05$; **: $P < 0.001$.

Figure 3 The expression of LASP1 in NPC cell lines



Notes: a; LASP1 mRNA level was significantly higher after transfection; b; The quantification results of transwell invasion and migration assay (*: $P < 0.001$); Representative images of transwell migration (c) and invasion (d) assays.

Figure 4 LASP1 over-expression increased SUNE1 cell migration and invasion *in vitro*



Notes: a; LASP1 mRNA level was significantly downregulated after transfected with shRNA; b; The quantification results of transwell invasion and migration assay (*: $P < 0.001$); Representative images of transwell migration (c) and invasion (d) assays.

Figure 5 LASP1 knockdown inhibited SUNE1 cell migration and invasion *in vitro*

3 讨论

我国是鼻咽癌高发国家。现有放化疗综合治疗模式下,局部复发和远处转移是鼻咽癌治疗失败的主要原因^[16,17]。因此寻找鼻咽癌复发转移相关关键分子,将为指导临床治疗提供新的分子靶点。LASP1是细胞运动过程中的关键蛋白分子。研究者前期研究发现,miR-203a-3p可在鼻咽癌中下调LASP1表达从而发挥肿瘤抑制作用^[15]。然而LASP1在鼻咽癌预后预测中的价值还未有报道。因此,若能明确LASP1表达与鼻咽癌患者临床参数的关系,可为进一步揭示鼻咽癌进展、转移的分子机制提供理论依据。

LASP1在多种恶性肿瘤表达升高,如乳腺癌^[8,18,19]、结肠癌^[10,14,20]、胰腺癌^[21]和胶质瘤^[11]。Gao等^[22]在60例鼻咽癌组织标本中发现LASP1在癌组织中高表达,且LASP1高表达患者OS差。本研究在79例鼻咽癌和10例癌旁组织中进一步验证此结果。不仅如此,本研究结果还表明,LASP1高表达患者OS、DMFS、RFS均显著差于LASP1低表达患者,提示LASP1在鼻咽癌发生进展过程中可能有重要功能,有可能为鼻咽癌诊断和治疗提供新的治疗靶点。另外,多因素分析发现LASP1高表达与TNM分期是患者OS的独立预后因子,提示LASP1表达高低与TNM分期一样,能对鼻咽癌患者预后的好坏进行鉴别。进一步需要研究明确LASP1是否能作为TNM分期的补充,用于鼻咽癌患者预后甄别。

LASP1是细胞支架蛋白的组成之一,介导细胞迁移生理过程^[23]。前期报道LASP1多在胞浆表达,其结构上包含LIM、NR和SH3结构域,这些结构域可以和众多蛋白结合,例如CXCR1、CXCR2和Vimentin等,参与肿瘤细胞和间质细胞的迁移过程^[24-26]。近期有研究发现LASP1在进展期乳腺癌组织中高表达于细胞核而在胞浆或包膜表达缺失,进一步研究发现CXCR12可促进LASP1细胞核转位从而启动细胞内甲基化过程^[8]。本研究中,LASP1主要表达于鼻咽癌细胞胞浆中,提示LASP1在鼻咽癌细胞中可能以细胞骨架蛋白通过结合其他功能蛋白发挥功能。

本研究也有一定局限性。首先,本研究是一项回顾性分析研究,样本量较小,需要进一步扩大样本量

验证。不仅如此,对于LASP1如何在鼻咽癌中发挥促进肿瘤细胞迁移、侵袭等功能,需要进一步实验筛选和验证LASP1可能发挥功能的分子机制。

综上所述,本研究发现,LASP1在鼻咽癌中显著高表达,LASP1高表达患者的生存较低表达患者差,LASP1表达是鼻咽癌患者OS独立预后因子。本研究结果提示LASP1作为肿瘤促进因子参与鼻咽癌进展过程,可能为LASP1应用于临床指导鼻咽癌治疗提供理论依据。

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