



# Plectin通过诱导F-actin聚合增强肝癌细胞的迁移能力\*

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**【摘要】** 目的 研究Plectin的表达与肝癌细胞迁移能力的关系,揭示Plectin表达影响肝癌细胞迁移行为的分子机理。方法 首先,Western blot检测正常肝细胞和肝癌细胞中Plectin的表达。其次,构建Plectin下调的肝癌细胞株,设立对照组(shNC组)和shPLEC组,各组分别设溶剂对照组(shNC+DMSO组或shPLEC+DMSO组)和F-actin骨架聚合诱导剂Jasplakinolide组(shNC+Jasp组或shPLEC+Jasp组)。采用Western blot检测各组肝癌细胞中Plectin的表达及上皮-间质转化(epithelial-mesenchymal transition, EMT)相关分子(N-cadherin、vimentin和E-cadherin)的表达;采用Transwell小室法分析肝癌细胞的迁移能力;采用KEGG(Kyoto Encyclopedia of Genes and Genomes)分析与Plectin基因有关的信号通路;采用免疫荧光技术检测Plectin表达变化对细胞骨架F-actin聚合的影响。结果 与正常肝细胞相比,Plectin在肝癌细胞中高表达。与shNC组相比,shPLEC组Plectin的表达降低( $P<0.05$ ),肝癌细胞的迁移能力减弱( $P<0.05$ ),EMT进程被抑制(N-cadherin和vimentin表达降低,E-cadherin表达升高)( $P<0.05$ );KEGG分析发现细胞骨架F-actin调控与Plectin的联系最为密切,shPLEC组肝癌细胞骨架F-actin发生解聚。采用F-actin骨架聚合诱导剂Jasplakinolide处理后,与shPLEC+DMSO组相比,shPLEC+Jasp组肝癌细胞迁移能力增强( $P<0.05$ ),EMT进程有所恢复(N-cadherin和vimentin表达升高,E-cadherin表达降低)( $P<0.05$ ),同时肝癌细胞骨架F-actin聚合亦有所恢复。结论 Plectin在肝癌细胞中高表达,肝癌细胞中Plectin通过诱导F-actin聚合促进肝癌细胞的迁移和EMT。

**【关键词】** Plectin 肝癌细胞 细胞迁移分析 上皮-间质转化 细胞骨架 F-actin

**Plectin Promotes the Migration of Hepatocellular Carcinoma Cells Through Inducing F-actin Polymerization** XU Rushuang<sup>1</sup>, YANG Lingxiao<sup>2</sup>, SONG Guanbin<sup>1△</sup>. 1. College of Bioengineering, Chongqing University, Chongqing 400030, China; 2. The Sixth People's Hospital of Chongqing, Chongqing 400060, China

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**【Abstract】 Objective** To explore the relationship between the expression of plectin and the migration of hepatocellular carcinoma (HCC) cells and to elucidate the molecular mechanisms by which plectin expression affects the migration of HCC cells. **Methods** First of all, Western blot was performed to determine the expression of plectin in normal hepatocytes and HCC cells. Secondly, a plectin-downregulated HCC cell strain was established and the control group (shNC group) and shPLEC group were set up. Each group was divided into a vehicle control group (shNC+DMSO group or shPLEC+DMSO group) and a F-actin cytoskeleton polymerization inducer Jasplakinolide group (shNC+Jasp group or shPLEC+Jasp group). Western blot was performed to determine the expression of plectin and epithelial-mesenchymal transition (EMT)-related proteins, including N-cadherin, vimentin, and E-cadherin. HCC cell migration was evaluated by Transwell assay. KEGG (Kyoto Encyclopedia of Genes and Genomes) was used to analyze the signaling pathways related to plectin gene. The polymerization of F-actin was analyzed by immunofluorescence assay. **Results** Compared with the normal hepatocytes, HCC cells showed high expression of plectin. Compared with those in the shNC group, the expression of plectin in the shPLEC group was decreased ( $P<0.05$ ), the migration ability of HCC cells was weakened ( $P<0.05$ ), and the EMT process was inhibited (with the expression of N-cadherin and vimentin being decreased and the expression of E-cadherin being increased) ( $P<0.05$ ). KEGG analysis showed that the regulation of cytoskeletal F-actin was most closely associated with plectin and cytoskeletal F-actin depolymerized in the shPLEC group. After treatment with Jasplakinolide, an inducer of F-actin cytoskeleton polymerization, the migration ability of HCC cells in the shPLEC+Jasp group was enhanced compared with that of shPLEC+DMSO group ( $P<0.05$ ) and the EMT process was restored (with the expression of N-cadherin and vimentin being increased and the expression of E-cadherin being decreased) ( $P<0.05$ ). In addition, the polymerization of cytoskeletal F-actin in HCC cells was also restored. **Conclusion** Plectin is highly expressed in HCC cells. Plectin promotes the migration and the EMT of HCC cells through inducing F-actin polymerization.

**【Key words】** Plectin Hepatocellular carcinoma cells Cell migration assays Epithelial-mesenchymal transition Cytoskeleton F-actin

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据2020年全球癌症统计数据,肝癌是全球第六大常见癌症,也是癌症相关死亡的第三大原因,在亚洲(尤其是中国),肝癌的发病率和死亡率均名列前茅<sup>[1]</sup>。截至目前,临床上针对肝癌患者治疗的首要手段仍然是手术结合其他放化疗,但临床上肝癌患者预后差、复发转移率高、5年生存率低的境况仍未改变<sup>[2-4]</sup>。因此,深入探讨肝癌发生及演进的机理对于临床肝癌的诊断和治疗具有重要意义。

肝癌细胞的迁移对于肝癌发生发展过程起着至关重要的作用<sup>[5]</sup>。上皮-间质转化(epithelial-mesenchymal transition, EMT)是上皮细胞获得间质特征并具有主动侵袭迁移能力的过程,这一过程主要包括上皮细胞间连接丢失、细胞骨架重组、细胞间接触蛋白如上皮标志物E-cadherin下调和间质标志物N-cadherin等上调以及细胞形态的改变等<sup>[5-6]</sup>。研究证实,肝癌细胞经历EMT后,肝癌细胞的迁移能力增加,具有更强的侵袭转移特性<sup>[7]</sup>。因此,EMT与肝癌细胞的迁移能力以及肝癌的发生发展密切相关。

Plakin蛋白家族在维持细胞骨架的完整性方面发挥着重要作用,并参与了细胞的多种生物学过程<sup>[8]</sup>。其中,Plectin作为近年来备受关注的高分子量、多结构域蛋白,它的不同亚型在皮肤、肌肉等组织中含量丰富。研究表明,Plectin作为维持细胞骨架和细胞形态完整性的主要成分,主要通过调节细胞骨架动力学和参与细胞间连接或细胞-基底连接调控细胞的生物学行为<sup>[9]</sup>。近年来,Plectin在肿瘤发生发展中的作用越来越受到人们的重视。研究发现,Plectin在胰腺癌、卵巢癌、前列腺癌等肿瘤中表达上调并可作为肿瘤标记物<sup>[10-11]</sup>,且能有效地调节这些肿瘤细胞的迁移侵袭行为。Plectin可以为各种信号分子提供支架平台,例如非受体酪氨酸激酶Src和Pyk2,丝氨酸/苏氨酸蛋白激酶Fer、AMP活化蛋白激酶和蛋白激酶A等<sup>[5]</sup>。此外,一项基于iTRAQ(Isobaric Tags for Relative and Absolute Quantitation)技术的研究证实Plectin可能与肝癌的侵袭转移相关<sup>[12]</sup>,但Plectin的表达是否影响肝癌细胞迁移及其分子机理尚不清楚。为此,本文首先分析了Plectin在正常肝细胞和肝癌细胞中的表达差异,然后研究了Plectin的表达与肝癌细胞迁移能力和EMT的关系,并进一步探究了Plectin表达改变影响肝癌细胞迁移行为和EMT进程的分子机理。

## 1 材料与方法

### 1.1 细胞培养

人正常肝细胞HL7702(L02)和人肝癌细胞HCCLM3、HepG2、MHCC97H、MHCC97L以及人肾上

皮细胞293T,均购自中国科学院上海细胞库,由本实验室传代保存。各细胞系均使用含10%胎牛血清(Gibco, USA)的H-DMEM高糖培养基,于37℃、体积分数为5%CO<sub>2</sub>培养箱中按常规方法培养及传代。

### 1.2 Plectin下调细胞株的构建

质粒系统包括pLKO.1-EGFP-PURO-PLEC(Unibio, Hunan, China)、psPAX2(Invitrogen, CA, USA)和pMD2.G(Invitrogen, CA, USA)用于慢病毒感染。首先质粒混合后加至293T细胞中,轻轻摇匀后在孵箱中培养48h,收集未纯化的病毒液,-80℃冰箱保存。然后在12孔板中培养约1×10<sup>4</sup>个肝癌细胞/孔(MHCC97H/MHCC97L),用收集的病毒液感染肝癌细胞,并加入8μg/mL polybrene(Sigma Aldrich, MO, USA)以提高感染率。培养48h后,倒置荧光显微镜观察细胞荧光强度。然后加入2μg/mL嘌呤霉素,筛选稳定克隆1周。最后用Western blot检测目的蛋白的表达情况。shRNA基因沉默质粒的靶序列如下:shNC:5'-CCTAAGGTTAAGTCGCCCTCGCTCGAGCGAGGGCGACTTAAACCTTAGG-3';shPLEC-1:5'-GCCUCUCAAUGCCAUCAUTTAUGAUGGCAUUGAAGAGGCTT-3';shPLEC-2:5'-GCCAGUACAUCAGUUAUTTAUGAACUUGAUGUACUGGCTT-3'。

### 1.3 细胞分组

细胞分组情况:①shNC组和shPLEC组:分析Plectin下调后对肝癌细胞的增殖、迁移能力、EMT进程和细胞骨架F-actin聚合的影响;②shNC+DMSO(体积分数0.1%)组、shNC+Jasp(20nmol/L)组、shPLEC+DMSO(体积分数0.1%)组和shPLEC+Jasp(20nmol/L)组:分析F-actin骨架聚合诱导剂Jasplakinolide(Jasp, ab141409, Abcam, UK)处理后对Plectin下调抑制肝癌细胞迁移能力和EMT进程、抑制细胞骨架F-actin聚合的逆转作用。

### 1.4 蛋白免疫印迹检测 Plectin、N-cadherin、vimentin和 E-cadherin的表达

使用蛋白裂解液(Beyotime, Shanghai, China)提取总蛋白,沸水变性10min。每孔加样30μg,调节电压至80V后电泳40min,再调节电压至120V使溴酚蓝跑到底。各抗体转膜条件为27V、13h(Plectin, ab32528, Abcam, UK)或200mA、90min(N-cadherin, ab76011, Abcam, UK; vimentin, ab92547, Abcam, UK; E-cadherin, ab40772, Abcam, UK; GAPDH, bsm-33033M, Bioss, China)。转膜结束后,放入5%脱脂奶粉中封闭1h。然后使用上述抗体4℃孵育过夜。TBST漂洗结束后,用对应的二抗孵育目的条带。TBST洗涤后,使用ECL印迹分析系统(Bio-OI, Guangzhou, China)进行显色。图片导入

Quantity one软件进行灰度值分析。

### 1.5 细胞增殖能力分析

取对数生长期细胞,进行离心后用1 mL培养基重悬、计数,调节细胞密度为 $3 \times 10^4 \text{ mL}^{-1}$ 。取100  $\mu\text{L}$ (即3 000个细胞)接种至96孔板中,轻轻摇匀后置孵箱中培养。分别在24 h、48 h和72 h向孔中加入10  $\mu\text{L}$  CCK8溶液,于孵箱中继续培养3 h。然后将孔板取出置于酶标仪中,设置波长为450 nm并测量光密度(optical density, OD)值,数据导入Origin 8.5 pro软件中进行统计作图,分析细胞的增殖能力。

### 1.6 Transwell迁移分析

取对数生长期的细胞进行消化后,使用无血清培养基调整细胞密度至 $2 \times 10^5 \text{ mL}^{-1}$ ,将100  $\mu\text{L}$ 细胞悬液接种于孔径8  $\mu\text{m}$ 的Transwell小室(Millipore, MA, USA)上室中,下室加入600  $\mu\text{L}$ 含10%胎牛血清的培养基作为诱导剂。37  $^{\circ}\text{C}$ 、体积分数为5%  $\text{CO}_2$ 条件下培养24h后,用棉签擦拭上室内培养基和未迁移细胞,室温下用体积分数4%多聚甲醛固定20 min,0.1%结晶紫染色液30 min。蒸馏水清洗残留的结晶紫,并于室温下晾干残余水分。在显微镜下观察视野内Transwell小室迁移的细胞并随机选取5个视野拍照。图片导入Image J软件进行计数,计算每个区域的迁移细胞数并取平均值。

### 1.7 生物信息学分析与Plectin基因有关的信号通路

使用KEGG(Kyoto Encyclopedia of Genes and Genomes)分析分子信号通路。本研究中,通过cbiportal(<https://www.cbiportal.org/>)查找与Plectin相关的共表达基因,然后使用在线数据分析库Sangerbox 3.0进行数据分析处理。满足 $P < 0.05$ 则定义为与Plectin基因显著相关的通路。

### 1.8 免疫荧光实验检测Plectin表达变化对细胞骨架F-actin聚合的影响

采用F-actin骨架聚合诱导剂Jasplakinolide(Jasp, 20 nmol/L)对转染细胞进行处理24 h,同时对对照组添加体积分数0.1%的DMSO。用体积分数4%多聚甲醛固定24孔板中的细胞30 min, PBS润洗3次。加入0.1% Triton-X-100破膜处理10 min, PBS润洗3次。用1%BSA室温封闭1 h后,每孔加入200  $\mu\text{L}$ 鬼笔环肽染色细胞骨架,4  $^{\circ}\text{C}$ 过夜孵育, PBS润洗3次。每孔加入200  $\mu\text{L}$  DAPI(Biosharp, Beijing, China)染色10 min, PBS润洗3次。倒置荧光显微镜(Leica, Solms, Germany)进行观察拍照。

### 1.9 统计学方法

所有数据均以 $\bar{x} \pm s$ 表示,每个实验至少重复3次。采用单因素方差分析(ANOVA)和 $t$ 检验。统计分析结果

采用 Origin 8.5 pro 软件绘制统计图。 $P < 0.05$ 为差异有统计学意义。

## 2 结果

### 2.1 Plectin在肝癌细胞中高表达

本研究首先分析了4种肝癌细胞系(HCCLM3、HepG2、MHCC97H和MHCC97L)和正常肝细胞系L02中Plectin的蛋白表达。Western blot分析结果显示,肝癌细胞中Plectin蛋白表达均高于正常肝细胞L02。而在肝癌细胞中,MHCC97H细胞中Plectin的表达高于其他肝癌细胞(图1)。

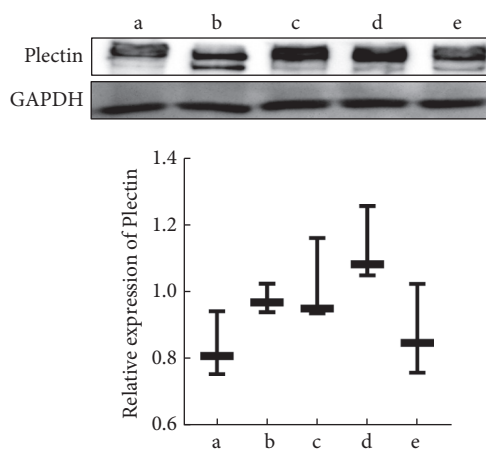


图1 人肝细胞与肝癌细胞中Plectin表达分析

Fig 1 Analysis of the Plectin expression in human liver cells and hepatocellular carcinoma cells

a: L02; b: HCCLM3; c: HepG2; d: MHCC97H; e: MHCC97L.  $n=3$ .

### 2.2 Plectin下调肝癌细胞株构建

本研究根据Plectin表达情况选择MHCC97H和MHCC97L两种肝癌细胞,采用慢病毒感染建立Plectin下调肝癌细胞株。结果如图2所示,与对照组比较,两种细胞敲减组Plectin表达显著下调,表明Plectin下调肝癌细胞株构建成功。根据Western blot中显示的Plectin敲减结果,本文选择shPLEC-1进行后续实验。

### 2.3 Plectin下调抑制肝癌细胞的迁移能力和EMT进程

细胞增殖实验结果显示,与shNC组相比,shPLEC组中两种肝癌细胞的增殖能力均无明显变化(图3A),提示Plectin下调不影响肝癌细胞的增殖。Transwell实验结果显示,与shNC组相比,shPLEC组中两种肝癌细胞的迁移能力均明显下降(图3B),提示Plectin下调抑制肝癌细胞的迁移。

本研究进一步探究了Plectin下调对肝癌细胞EMT的影响。结果显示,两种肝癌细胞的Plectin下调后,间质标志分子N-cadherin和vimentin表达显著降低,而上皮标志

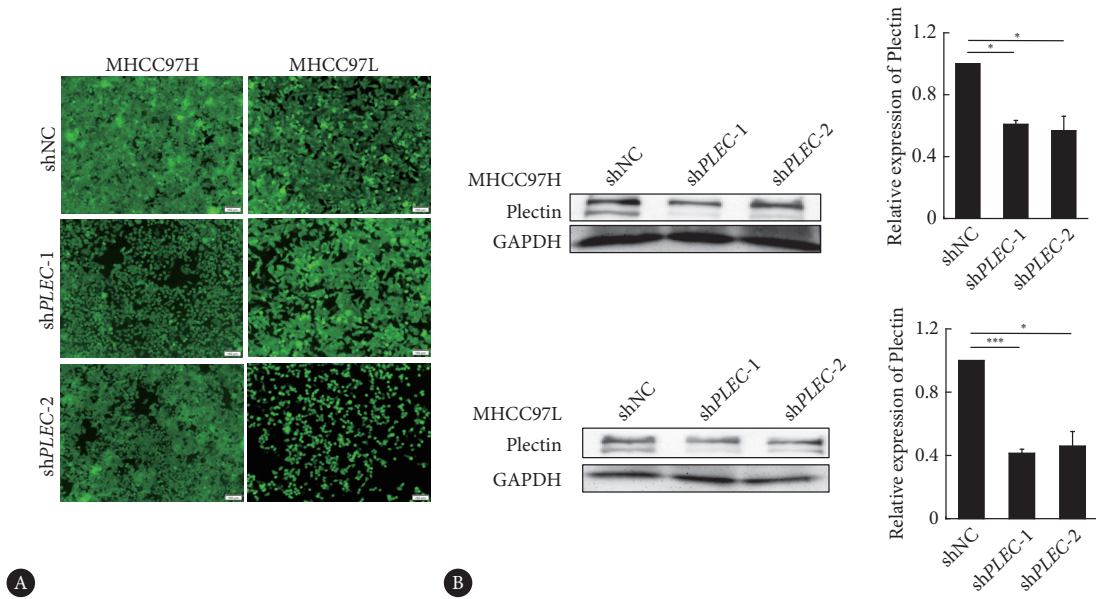


图 2 Plectin 下调肝癌细胞株构建

Fig 2 Construction of Plectin-downregulated HCC cell lines

A, Immunofluorescence assay was performed to determine the infection efficiency of lentivirus (scale bar=100 μm); B, Western blot was performed to determine the knockdown efficiency of Plectin. n=3. \* P<0.05, \*\*\* P<0.001.

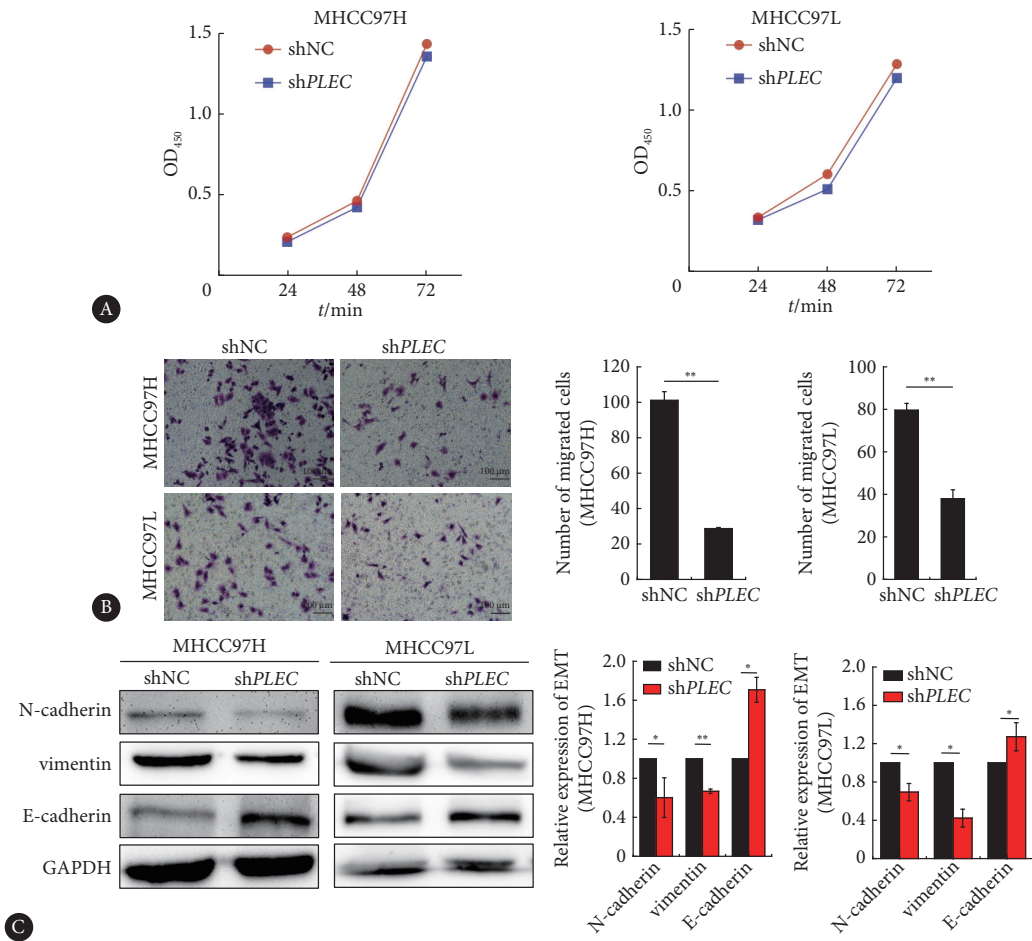


图 3 Plectin 下调对肝癌细胞增殖 (A)、迁移 (B) 和 EMT 进程 (C) 的影响

Fig 3 Effect of Plectin downregulation on the proliferation (A), migration (B, scale bar=100 μm) and EMT (C) of HCC cells

n=3. \* P<0.05, \*\* P<0.01.

分子E-cadherin表达显著升高(图3C),提示Plectin下调抑制了肝癌细胞的EMT。

#### 2.4 Plectin下调抑制细胞骨架F-actin的聚合

本研究采用生物信息学技术分析了Plectin相关信号通路,结果发现细胞骨架F-actin调控与Plectin的联系最为密切(图4A)。免疫荧光染色结果显示,Plectin下调后肝癌细胞F-actin的荧光强度明显降低,丝状纤维束数量减

少,骨架结构松散(图4B),提示Plectin下调抑制了肝癌细胞F-actin的聚合。进一步研究显示,与shPLEC+DMSO组相比,shPLEC+Jasp组中F-actin荧光强度明显增强,丝状纤维束更粗、数量更多,骨架结构更清晰(图4C)。结果证实,Plectin下调抑制了肝癌细胞骨架F-actin的聚合,Jasp处理能一定程度上逆转Plectin下调抑制的F-actin聚合。

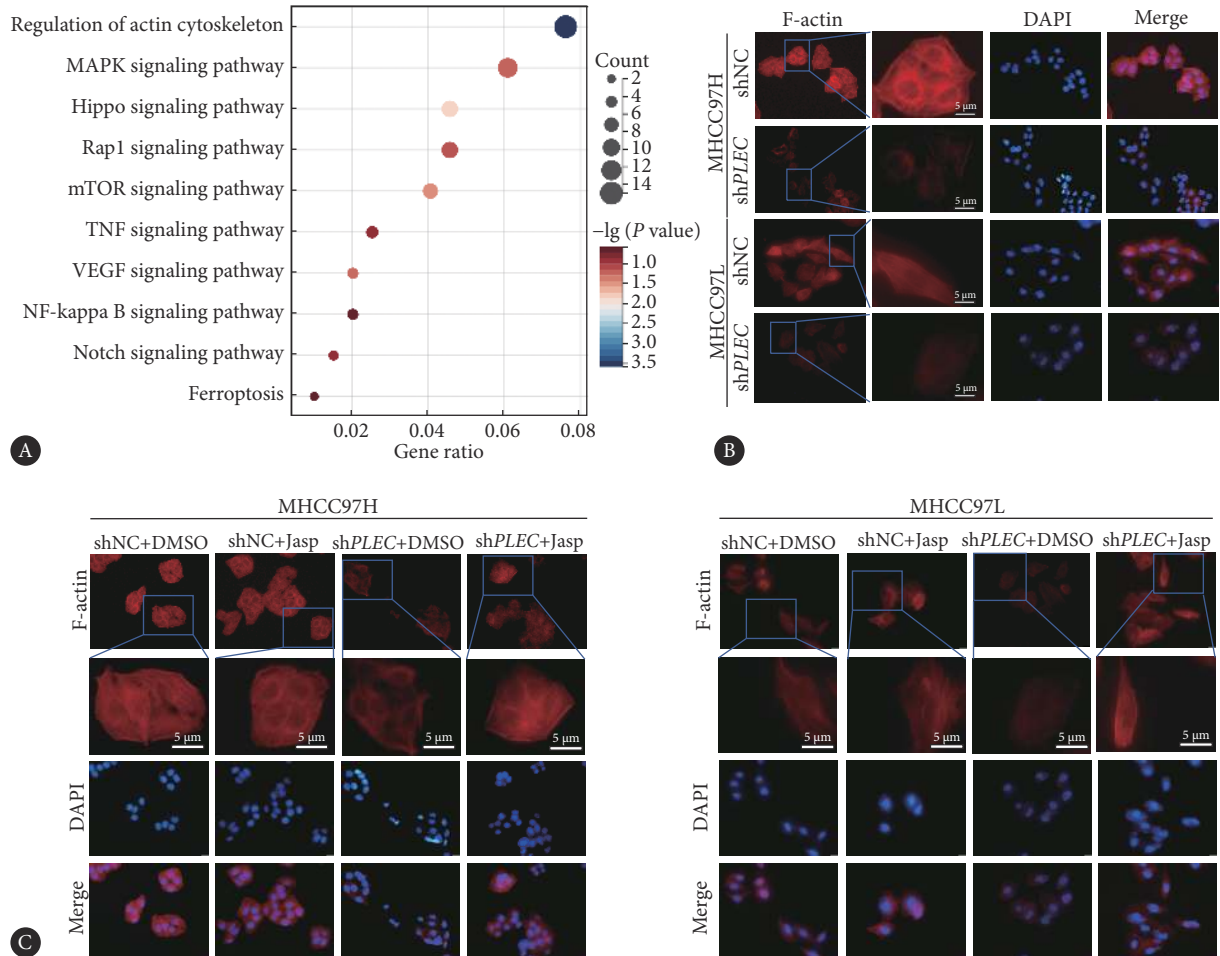


图 4 Plectin下调抑制肝癌细胞骨架F-actin的聚合

Fig 4 Plectin downregulation inhibites polymerization of cytoskeleton F-actin in HCC cells

A, KEGG enrichment analysis of Plectin-related signaling pathways; B, changes of F-actin in HCC cells after Plectin downregulation (scale bar=100  $\mu\text{m}$ ); C, effect of Jasp treatment on the F-actin polymerization of HCC cells (scale bar=100  $\mu\text{m}$ ).

#### 2.5 Plectin下调通过解聚F-actin抑制肝癌细胞迁移和EMT

Transwell结果显示,与未处理组比较,Jasp处理后肝癌细胞的迁移能力显著回升(图5A)。此外,Western blot结果显示,相比于未处理组,Jasp处理后促进了肝癌细胞间质标志分子N-cadherin和vimentin的蛋白表达,抑制了上皮标志分子E-cadherin的蛋白表达(图5B)。结果表明,Jasp处理诱导F-actin聚合,部分逆转了因Plectin下调抑制的肝癌细胞迁移能力和EMT进程。

### 3 讨论

Plectin作为一种细胞骨架连接蛋白,将中间丝与微丝、微管交联,维持细胞骨架网络的完整性,是一种关键的细胞张力稳态和力信号转导调节因子。近年来,人们发现Plectin在肿瘤组织中异常表达,在肿瘤发生和演进中起重要作用。本研究考察了Plectin在肝癌细胞中的表达及其对肝癌细胞迁移能力的影响,证实肝癌细胞中Plectin呈现高表达,并通过诱导F-actin聚合促进肝癌细胞

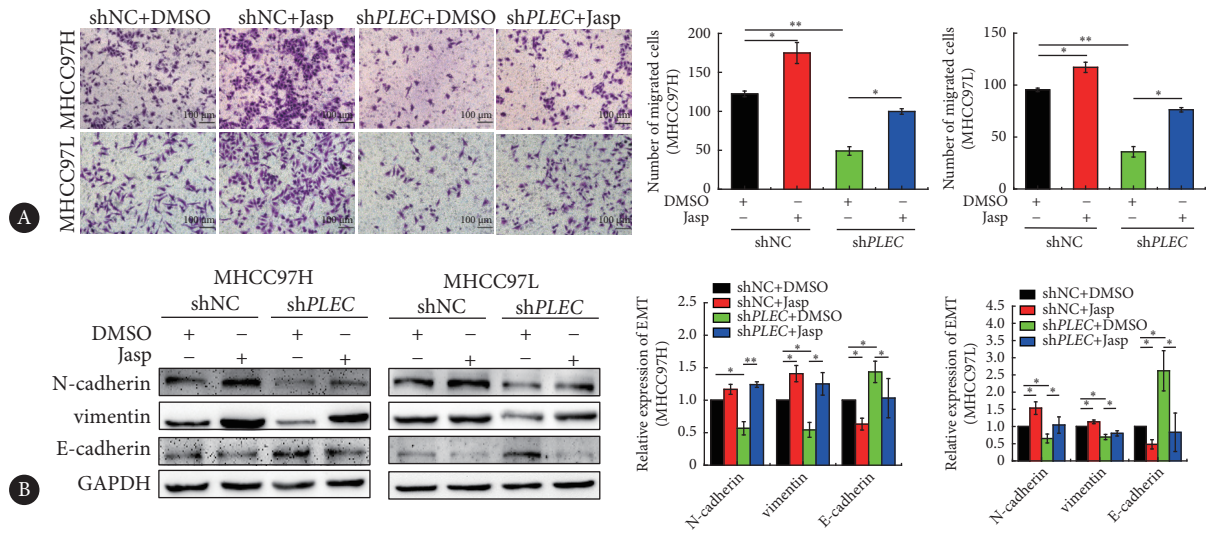


图 5 Jasp处理回救Plectin下调抑制的肝癌细胞迁移 (A) 和EMT进程 (B) 在HCC细胞

Fig 5 Jasp treatment restored Plectin downregulation-suppressed migration (A, scale bar=100 μm) and the EMT process (B) in HCC cells

n=3. \* P<0.05, \*\* P<0.01.

的迁移和EMT进程,提示肝癌细胞中Plectin异常表达在肝癌演进中扮演重要角色。

细胞通过细胞骨架与外界环境发生错综复杂的联系,细胞骨架收缩产生的张力可以感知细胞外基质的力学特性<sup>[13-14]</sup>。Plectin可通过细胞骨架、黏着斑、桥粒、核膜等向细胞核传递信号,最终引起细胞力学生物学行为的改变<sup>[15-16]</sup>。如果Plectin缺乏或减少,细胞中间丝非常不稳定,进而造成中间丝锚定的半桥粒等复合物结构和功能变化。例如,在皮肤角质形成细胞中,半桥粒的稳定依赖于Plectin介导的中间丝动态网络<sup>[17-18]</sup>。研究证实,中间丝波形蛋白vimentin在多种肿瘤细胞中表达上调,并诱导细胞发生形态和运动的变化,已被公认为是细胞EMT进程中的间质标志物<sup>[19]</sup>。本研究发现,肝癌细胞中Plectin下调后,会下调肝癌细胞中vimentin的表达,另一种间质标志物N-cadherin也出现下调,但上皮标志物E-cadherin表达上调,表明Plectin高表达不仅增强肝癌细胞的迁移能力,而且促进了肝癌细胞的EMT进程。

Plectin可以与肌动蛋白和微管结合并影响细胞骨架系统的力学特性和动态特征<sup>[20]</sup>。肌动蛋白介导细胞片状伪足、丝状伪足、应力纤维和黏着斑等结构的形成,直接参与细胞迁移、胞质分裂、细胞内物质运输和内吞作用等多种力学生物学行为。肌动蛋白应力纤维被认为是细胞硬度的重要调节成分<sup>[21]</sup>。有研究报道,Plectin表达下调降低了小鼠成肌细胞的细胞硬度、黏附强度和应激能力,并削弱细胞对胞外力信号的感知和传递<sup>[22]</sup>。在小鼠成纤维细胞中,Plectin缺乏会导致其肌动蛋白应力纤维和黏着斑数量改变,降低细胞运动能力<sup>[23]</sup>。本研究也证实,肝

癌细胞中Plectin下调使F-actin解聚,应力纤维数量减少,导致细胞迁移能力降低和EMT进程阻滞。这些结果提示,Plectin可以通过影响F-actin的解聚或聚合调控细胞的力学生物学行为,其相互作用可能在细胞响应微环境变化的信号转导中发挥重要作用。

在肝癌的发生过程中,通常肝脏首先发生炎症,然后出现肝纤维化、肝硬化和门脉高压等临床特征,最后演变成肝癌。因此,从纤维化到硬化再到肝癌,是肝癌发生的典型过程,肝癌组织呈现明显的力学微环境改变<sup>[24]</sup>。有研究报道,肝癌组织的硬度远远大于正常肝组织<sup>[25]</sup>。本课题组前期研究也证实,肝脏病变过程不仅呈现典型的力学特性改变,而且肝癌组织的不同区域也表现出力学异质性<sup>[26]</sup>。这些结果提示,肝脏组织力学微环境的变化在肝癌发生发展过程中起重要作用。本研究发现肝癌细胞中Plectin高表达并调节其迁移和EMT,Plectin是否是感知肝脏病变中力学微环境变化的力敏感分子,还需进一步的实验探究。但本研究结果证实了肝癌细胞中高表达的Plectin通过细胞骨架F-actin聚合促进其迁移和EMT,这为深入认识Plectin调控肝癌细胞的力学生物学行为以及在肝癌发生发展中的作用提供了实验依据,也为临床上寻求肝癌治疗的新靶点提供了理论基础。

\* \* \*

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