DOI:10.16016/j.2097-0927.202504029

ETS1转录上调FBXO45通过EMT而促进肝癌的侵袭迁移

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[摘要] **目的** 探究E26转化特异性转录因子1(E26 transformation-specific 1,ETS1)和F-盒蛋白45(F-box protein 45,FBXO45)在人肝癌细胞中侵袭转移的影响和潜在的分子机制。**方法** 采用Jaspar、hTFtarget、Cistrome转录因子数据库预测网站预测FBXO45的转录因子。根据各个数据库预测的结果取交集,对筛选出的候选转录因子分别在高转移人肝癌细胞(high metastatic human hepatocellular carcinoma cell line, HCCLM3)和人肝癌细胞(human hepatocellular carcinoma cell line,Huh7)中敲低各个的基因表达后检测FBXO45的表达情况,选出对FBXO45表达影响最显著的一个分析并采用染色质免疫共沉淀(chromatin immunoprecipitation,ChIP)实验验证与FBXO45启动子的结合情况,确定FBXO45潜在的转录因子。在肝癌细胞HCCLM3和Huh7中过表达ETS1后通过Transwell实验检测其对肝癌细胞侵袭迁移的影响和通过Western blot检测上皮间充质转化(epithelial-mesenchymal transition,EMT)相关蛋白表达变化情况。在过表达ETS1情况下敲低FBXO45检测对其侵袭迁移能力的影响。**结果** 通过预测FBXO45转录因子后取交集筛选出3个候选转录因子,分别是ETS1、SPI1和YY1)。在HCCLM3和huh7细胞中分别敲低ETS1、SPI1和YY1,结果发现ETS1敲低后显著导致了FBXO45的表达降低($P<0.05$)。根据癌症基因组图谱(The Cancer Genome Atlas,TCGA)数据和基因表达综合数据库(Gene Expression Omnibus,GEO)数据的分析显示,ETS1和FBXO45表达水平呈显著正相关($R=0.31$,$P<0.000\ 1$;$R=0.40$,$P=0.021\ 9$)。ChIP实验结果提示,ETS1可以和FBXO45启动子序列特异性结合而调控其表达,证实了ETS1为FBXO45潜在的转录因子。然后在肝癌细胞HCCLM3和Huh7中过表达ETS1后发现细胞侵袭迁移能力明显增加,并上调了N-cadherin、Snail蛋白的表达($P<0.01$)。此外,在ETS1过表达的情况下敲低FBXO45后可以显著抑制其侵袭迁移能力($P<0.01$)。**结论** ETS1激活FBXO45的转录使其高表达而通过EMT途径增强肝癌细胞的侵袭和迁移,促进肝癌进展。

[关键词] 肝癌;E26转化特异性转录因子1;上皮间充质转化;侵袭转移
[中图法分类号] R394.3;R73-37;R735.7 [文献标志码] A

ETS1 transcription up-regulates FBXO45 and promotes invasion and migration of hepatocellular carcinoma *via* epithelial-mesenchymal transition

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[**Abstract**] **Objective** To explore the roles of transcription factor E26 transformation-specific 1 (ETS1) and F-box protein 45 (FBXO45) in invasion and metastasis in hepatocellular carcinoma cells and the

[基金项目] 国家自然科学基金青年科学基金项目
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引用格式:朱贞宝,吴飞繁,顾永鹏,等.ETS1转录上调FBXO45通过EMT而促进肝癌的侵袭迁移[J].陆军军医大学学报,2025,47(12):1332-1341.DOI:10.16016/j.2097-0927.202504029.
Citation:ZHU Z B, WU F F, GU Y P, *et al*. ETS1 transcription up-regulates FBXO45 and promotes invasion and migration of hepatocellular carcinoma via epithelial-mesenchymal transition[J]. J Army Med Univ,2025,47(12):1332-1341. DOI:10.16016/j.2097-0927.202504029.

potential molecular mechanism. **Methods** Jaspar, hTFtarget and Cistrome transcription factor database prediction websites were used to predict the transcription factors of FBXO45. According to the intersection of the predicted results of each database, the expression of FBXO45 was detected after the candidate transcription factors were knockdown in HCCLM3 and Huh7 liver cancer cells, respectively. The most significant influence on FBXO45 expression was selected for further analysis, and chromatin immunoprecipitation assay (ChIP) was used to verify the binding to the FBXO45 promoter. Finally, the potential transcription factor of FBXO45 was identified. The effect of ETS1 overexpression on invasion and migration in HCCLM3 and Huh7 cells was detected by Transwell assay, and the expression levels of epithelial-mesenchymal transition (EMT) pathway proteins were detected by Western blot assay. The effects of FBXO45 knockdown on the invasion and migration under the condition of overexpression of ETS1 were also studied. **Results** Intersection of FBXO45 transcription factors identified 3 candidate transcription factors, ETS1, SPI1 and YY1. When the 3 transcription factors were knocked down in HCCLM3 and Huh7 cells, respectively, ETS1 knockdown significantly reduced the expression of FBXO45. According to the analysis of The Cancer Genome Atlas (TCGA) data and the Gene Expression Omnibus (GEO) data, the expression levels of ETS1 and FBXO45 were significantly positively correlated (R=0.31, P<0.000 1; R=0.40, P=0.021 9). ChIP suggested that ETS1 could specifically bind to FBXO45 promoter sequence to regulate its expression, confirming that ETS1 was a potential transcription factor of FBXO45. After overexpression of ETS1 in HCCLM3 and Huh7 cells, the invasion and migration abilities of cells were significantly enhanced, and the expression of N-cadherin and Snail was up-regulated(P<0.01). In addition, in the case of ETS1 overexpression, FBXO45 knockdown significantly inhibited the invasion and migration(P<0.01). **Conclusion** ETS1 activates the transcription of FBXO45 and leads its high expression, which enhances the invasion and migration of HCC cells *via* EMT pathway and promotes the progression of hepatocellular carcinoma.

[**Key words**] hepatocellular carcinoma; E26 transformation-specific 1; epithelial-mesenchymal transition; invasion and migration

Supported by the National Natural Science Foundation of China Young Scientists Fund (82203780). Corresponding author: ZHANG Leida, E-mail: zld666@aliyun.com

原发性肝癌(hepatocellular carcinoma, HCC)是全球第六大常见恶性肿瘤和第三大癌症相关死亡原因,给各国健康和经济都带来了沉重的负担[1]。在过去几十年的发展中,虽然各种各样的治疗方法已经让肝癌的5年生存率得到明显提高,但因为其较高的复发转移率,HCC患者的预后仍然非常差,在传统的肝癌切除术后,5年复发转移率可高达70%[2-3]。所以研究HCC的转移机制并针对关键靶点开发新的治疗方法尤为重要。

转录因子ETS家族已被证明通过调节或参与各种信号通路、细胞增殖、分化、细胞凋亡、侵袭和转移等的基因表达而发挥各种重要的生物功能。E26转化特异性转录因子1(E26 transformation-specific 1, ETS1)是ETS转录因子家族的核心成员,具有高度保守的DNA结合结构域,即ETS结构域,可特异性识别DNA序列5′-GGAA/T-3′调控靶基因的表达[4]。ETS1在淋巴细胞中表达相对较高,对免疫细胞功能有调节作用,并且参与淋巴细胞的发育和分化[5-6],且在不同肿瘤的发生过程中起着促进或抑制肿瘤的作用[7-8]。既往研究报道[9]ETS1作为其他分子的下游靶基因间接的参与了肝癌的发生进展,但其是否直接单独转录调控下游分子的表达而影响肝癌的侵袭转移尚不明确。

F-盒蛋白45(F-box protein 45,FBXO45)是一种E3泛素连接酶,既往课题组曾报道了其在肝癌中高表达并导致不良预后[10],但FBXO45高表达原因暂不明确,推测其可能受到某上游转录因子的调控,为明确其高表达原因,本研究通过多个转录因子预测网站预测了FBXO45的可能转录因子,并筛选出ETS1是其潜在的转录因子,接着分析了ETS1与FBXO45二者在肝癌侵袭转移中的作用以及对相关通路蛋白表达的影响,为治疗转移性肝癌提供新的靶点和理论依据。

1 材料与方法

1.1 生物信息学分析

转录因子预测:利用Jaspar网站(https://jaspar.elixir.no),hTFtarget网站(https://guolab.wchscu.cn/hTFtarget)和Cistrome网站(http://cistrome.org/db/)进行转录因子预测。在这些网站的搜索栏中输入*FBXO45*基因,可获取预测的转录因子集合。对于Jaspar网站,需先在NCBI(www.ncbi.nlm.nih.gov)网站上获取基因的转录启动子序列,及基因上游2 000 bp区域为启动子区域。将启动子序列复制并输入Jaspar网站对应区域,以获得预测的转录因子集合。汇总不同网站的预测结果,并通过Venn图筛选出交集。选取交集中的转录因子进行进一步验证。

转录因子结合位点预测:在Jaspar网站中进行,在对应地方输入交集中的各个转录因子,选取合适相对分数阈值(relative score threshold,RST)后筛选,并在启动子序列中找到对应的区域。

癌症基因组图谱(The Cancer Genome Atlas,TCGA)数据库分析:进入TCGA数据库(https://www.cancer.gov/)下载肝癌转录组数据TPM值,筛选基因*ETS1*和*FBXO45*,然后对TPM值进行Log_2(TPM+1)处理并分析其相关性。

基因表达综合(Gene Expression Omnibus,GEO)数据库分析:进入GEO数据库(https://www.ncbi.nlm.nih.gov/geo/)下载肝癌转录组数据TPM值(数据库ID:GSE138485),处理方法同上。

1.2 细胞培养与传代

高转移人肝癌细胞(high metastatic human hepatocellular carcinoma cell line,HCCLM3)和人肝癌细胞(human hepatocellular carcinoma cell line,Huh7)购买自上海复旦细胞库,使用完全培养基按要求培养细胞(DMEM高糖培养液+10%胎牛血清,Gibco,美国)。培养环境为37 ℃,5% CO_2细胞培养箱。当细胞生长至合适密度时,用0.25% EDTA-胰蛋白酶(Gibco,美国)进行细胞消化、重悬后按实验所需传代,然后用合适量进行铺板进行下一步实验。

1.3 细胞转染

取生长合适的细胞先予以消化离心后铺板(6孔板),次日观察密度合适(约70%)可予以转染,采用OPTI-MEM(Gibco,美国)+Lipofectamine™2000转染试剂(Invitrogen,美国)进行转染,对应的干扰以及阴性对照(siCont组)用量10 μL,过表达ETS1质粒(OE-ETS1组)和空载对照质粒(对照组)用量3 μg。转染48 h后收细胞进行下一步实验。实验所需siRNA序列见表1。

表1 目的基因、3个转录因子对应siRNA序列

基因名称	干扰序列(5′→3′)
ETS1	正义链:ACUUGCUACCAUCCCGUAC-dTT
	反义链:GUACGGGAUGGUAGCAAGU-dTT
SPI1	正义链:UGAGAUAGGGGUAAUACUCGU
	反义链:GAGUAUUACCCCUAUCUCAGC
YY1	正义链:CCCCUUCGAUGGUUGUAAUAA
	反义链:UUAUUAACAACCAUCGAAGGGG
FBXO45	正义链:CAGAUAGGAGAAAGAAUUCGA
	反义链:UCGAAUUCUUUCUCCUAUCUG

1.4 逆转录实时定量聚合酶链式反应实验

根据试剂说明书进行实验,Trizol试剂(TaKaRa,日本)用于从组织或培养细胞中提取总RNA。使用逆转录试剂盒(TaKaRa,日本)逆转录获取cDNA。然后,采用TB Green(TaKaRa,日本)进行q-PCR。将上样完毕的96孔PCR板至于时定量聚合酶链式反应仪器中进行反应,每个样品3个副孔[反应程序:95 ℃,30 s;95 ℃,5 s;60 ℃,30 s(40次循环),4 ℃]。最后根据CT结果值和$2^{-\triangle\triangle Ct}$方法来计算基因的相对表达量。所用引物序列见表2。

表2 目的基因、内参基因、3个转录因子对应引物序列

基因名称	引物序列(5′→3′)
ETS1	上游:GATAGTTGTGATCGCCTCACC
	下游:GTCCTCTGAGTCGAAGCTGTC
SPI1	上游:GTGCCCTATGACACGGATCTA
	下游:AGTCCCAGTAATGGTCGCTAT
YY1	上游:ACGGCTTCGAGGATCAGATTC
	下游:TGACCAGCGTTTGTTCAATGT
FBXO45	上游:TTTCCACAGTGCAACAACGC
	下游:AAAGCCACTGTCATCCGTCC
β-actin	上游:GAGAAAATCTGGCACCACACC
	下游:GGATAGCACAGCCTGGATAGCAA

1.5 Western bolt实验

用蛋白酶抑制剂混合物(Roche,瑞士)+RIPA裂解缓冲液(Thermo Fisher,美国)从处理的细胞中提取总蛋白,然后在冰上孵育20 min。孵育后,将裂解液在4 ℃中13 000 r/min,离心15 min。离心后将上清液收集到新的EP管中。BCA蛋白质试剂盒(Beyotime,中国)用于量化蛋白质的浓度。然后金属浴100 ℃,10 min将蛋白变性,变性后将样品通过10%SDS-PAGE凝胶

电泳分离,然后转到NC膜(Amersham,美国)。将膜在室温下用5%脱脂牛奶封闭1 h,然后在4 ℃下与对应一抗孵育过夜。次日,洗膜后将膜与对应种属二抗在室温下孵育1 h后洗膜。使用ECL发光液(雅酶,中国)和凝胶成像系统(BIO-RAD,美国)对蛋白条带曝光显影拍照。所用一抗及稀释比例:FBXO45(BIOSS, Cat# bs-13150R,1∶1 000);N-cadherin(CST,Cat# 14215S,1∶5 000);Snail(CST,Cat# 3879S,1∶5 000);β-actin(三鹰,Cat# 20536-1-AP,1∶5 000)。

1.6 Transwell细胞侵袭和迁移实验

将处理好的细胞消化离心计数,200 μL无血清培养基中1×10^{5}个Huh7或6×10^{4}个HCCLM3细胞加入到上室中(侵袭实验中需要加入50 μL基质胶混合物,用DMEM以1∶8稀释)。然后将含有10% FBS的800 μL DMEM加入到下室中。在37 ℃下孵育24 h后取出,用棉签除去上室中的细胞,用4%甲醛固定下室表面上的细胞15 min,并用0.1%结晶紫染色30 min,3次生物学重复。使用EVOS XL核心成像系统(Thermo Fisher,美国)对迁移的细胞进行观察、拍照和人工计数统计分析。

1.7 染色质免疫共沉淀(chromatin immunoprecipitation, ChIP)实验

根据制造商的方案使用ChIP检测试剂盒(Beyotime,中国)。将培养好的适量细胞后用1%甲醛进行交联、细胞裂解、超声片段化染色质、染色质离心。然后使用ETS1抗体(ETS1 IgG组;CST,14069,5 μL)或同种属匹配的免疫球蛋白G(Normal IgG组;阴性对照,CST,3900S,5 μL),然后加入蛋白A/G珠中。DNA-蛋白质交联通过加热逆转,免疫沉淀的DNA进行qPCR扩增。3次生物学重复。所用特异性引物序列见表3。

表3 ChIP实验所需的FBXO45特异性引物序列

*FBXO45*基因	引物序列(5′→3′)
P1	上游:GCCAGAGCGCAGAATGAGAG
	下游:CTTTCACCTGCTCATCACCCA
P2	上游:TCTCTACAGGCTTGGGGTTT
	下游:TTCACCAAGTCCAGTAACCCT
P3	上游:ACCAAGGGAGTCTGTGAACC
	下游:ACCAAGGGAGTCTGTGAACC
P4	上游:GCCTCCACGTCATTCTCCCT
	下游:AAGTGCTGCCGTCTTTTGGA
P5	上游:GGAGCCACCAGACCAGAAAA
	下游:CGGGTGAGGTTATCACTAGGC

1.8 统计学分析

GraphPad Prism 8.0软件用于数据分析和图表制作。计量数据以$\bar{x}\pm s$的形式表示。2组间比较采用双尾非配对t检验。采用Pearson相关系数分析基因相关性,P<0.05认为差异有统计学意义。

2 结果

2.1 生物数据库网站预测FBXO45转录因子

为了分析FBXO45在肝癌中高表达原因,本研究通过3个人类转录因子预测网站Jaspar、hTFtarget、Cistrome进行分析,通过Venn图筛选出了3个可能的转录因子,分别是ETS1、SPI1和YY1(图1)。接着在Jaspar网站中导入FBXO45启动子序列,一般认为基因上游2 000 bp区域大致为该基因的启动子区域,然后分析预测了转录因子的结合位点在其基因启动子区域的占比情况,然后设置相对分数阈值(relative score threshold,RST),阈值越高筛选出结果相对较少,同时该序列为结合序列可能性越大,将阈值设置为90%,结果发现在相同阈值筛选下,ETS1与FBXO45启动子结合的位点最多。接着用siRNA在HCCLM3和Huh7肝癌细胞中分别敲低*ETS1*、*SPI1*、*YY1*基因(*siETS1*、*siSPI1*、*siYY1*),结果发现在敲低*ETS1*后使*FBXO45*表达下调最显著,在HCCLM3中下调约71.2%,在Huh7中下调约34.4%(P<0.05,图2),同时根据TCGA和GEO数据库分析显示ETS1和FBXO45表达呈显著正相关(R=0.31,P<0.0001;R=0.40,P=0.0219,图3)。综上,结果表明ETS1可能为FBXO45潜在的转录因子。

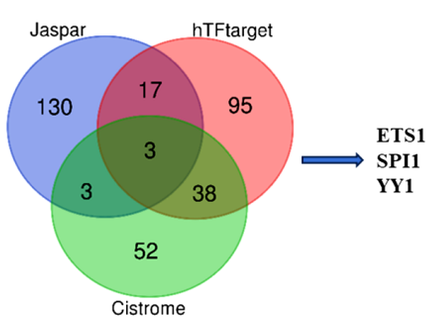
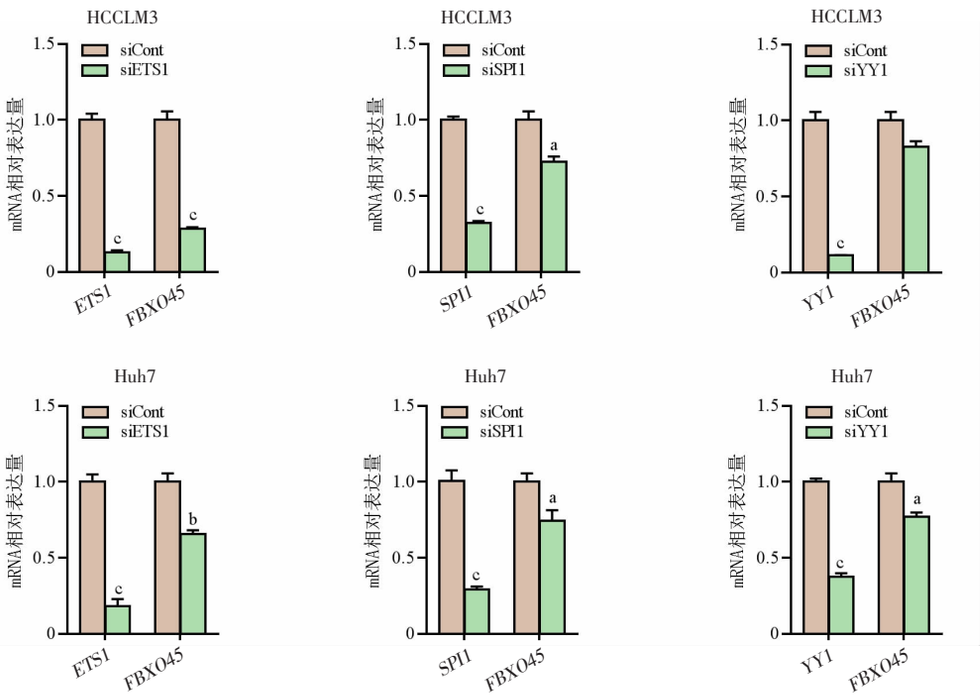


图1 3个网站预测的FBXO45转录因子进行筛选的Venn图

2.2 ETS1可特异性结合FBXO45启动子序列调控其表达

在敲低ETS1的基础上,分别在HCCLM3和Huh7中过表达ETS1(OE-ETS1组),结果发现,过表达ETS1后上调了FBXO45的表达,在HCCLM3和Huh7中分别上调1.87倍和2.06倍,(P<0.001,图4)。为了进一步



a:P<0.05,b:P<0.01,c:P<0.001,与siCont组比较

图2 分别敲低3个转录因子后qPCR检测FBXO45的mRNA表达

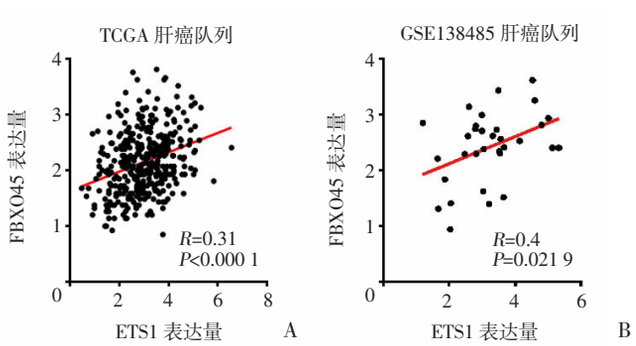
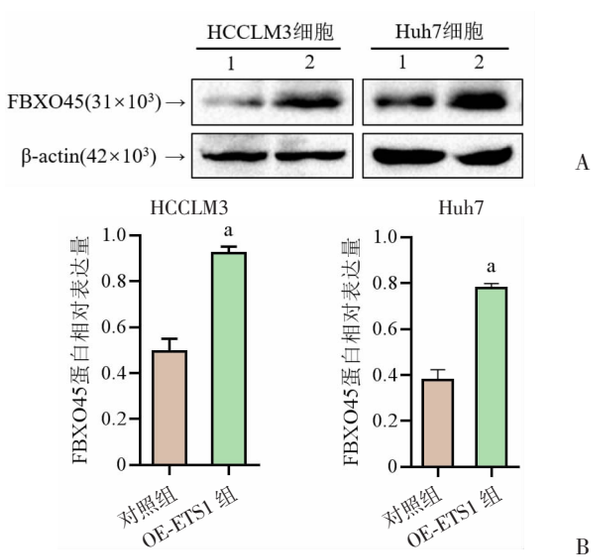


图3 TCGA(A)和GEO(B)数据库分析肝癌中ETS1和FBXO45表达的相关性

证明ETS1能转录调控FBXO45的表达,利用FBXO45启动子序列设计了5段引物P1~P5(图5),然后在HCCLM3细胞中进行ChIP实验,结果证实ETS1可通过与FBXO45启动子的结合而激活转录上调其表达(图6)。

2.3 ETS1通过上皮间充质转化(epithelial-mesenchymal transition,EMT)途径促进肝癌细胞侵袭转移

为了进一步明确ETS1对肝癌细胞侵袭转移的作用,通过Transwell实验分析了在HCCLM3和Huh7中过表达ETS1后对侵袭转移的影响。分别在HCCLM3和Huh7细胞中转染了空白对照质粒(对照组)和ETS1过表达质粒(OE-ETS1组),结果显示,相较于对照组,



1:对照组;2:OE-ETS1组;a:P<0.001,与对照组比较
A:Western blot检测FBXO45蛋白表达水平;B:蛋白表达水平相对定量分析

图4 HCCLM3和Huh7中过表达ETS1后对FBXO45蛋白表达水平的影响

OE-ETS1组肝癌细胞侵袭迁移能力显著提高,差异具有统计学意义(P<0.001,图7)。EMT途径是促进侵袭转移的重要通路,因此进一步通过Western blot实验检测了2组细胞的N-cadherin、Snail蛋白的表达水平,结果发现,相较于对照组,OE-ETS1组N-cadherin、Snail

的表达上调,在HCCLM3中分别上调1.72倍和1.84倍,在Huh7中分别上调1.92倍和2.00倍(P<0.05,图8)。提示ETS1可以激活EMT通路。

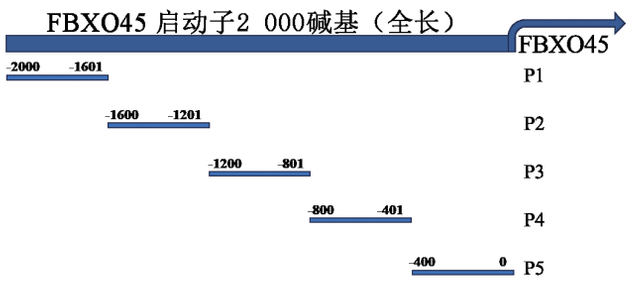
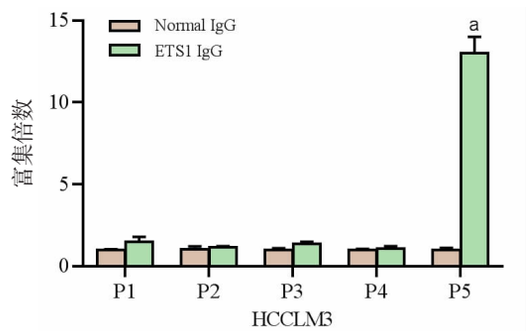


图5　FBXO45启动子示意图并根据序列设计5段引物

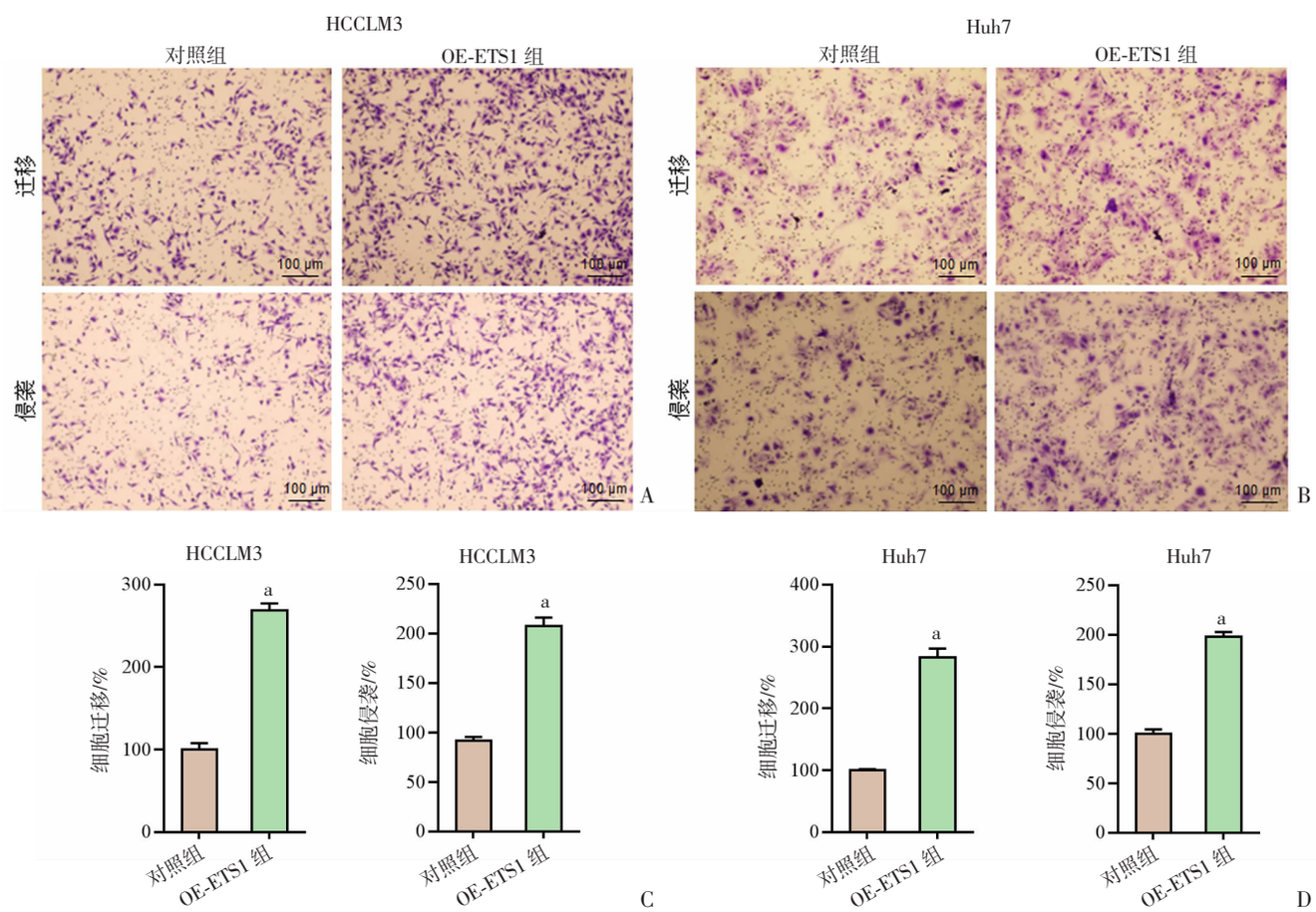
2.4　敲低FBXO45可以抑制ETS1所介导的肝癌细胞侵袭迁移

由于过表达ETS1可以上调FBXO45的表达,接下来为了研究FBXO45在ETS1促进肝癌细胞侵袭转移中的作用,在肝癌细胞中验证过表达ETS1情况下敲低FBXO45后对肝癌细胞侵袭迁移能力的影响(OE-ETS1+siFBXO45组)。结果发现,相较于OE-ETS1组,OE-ETS1+siFBXO45组显著逆转ETS1所介导的肝癌细胞的侵袭迁移(P<0.01,图9)。



a:P<0.01,与Normal IgG组比较

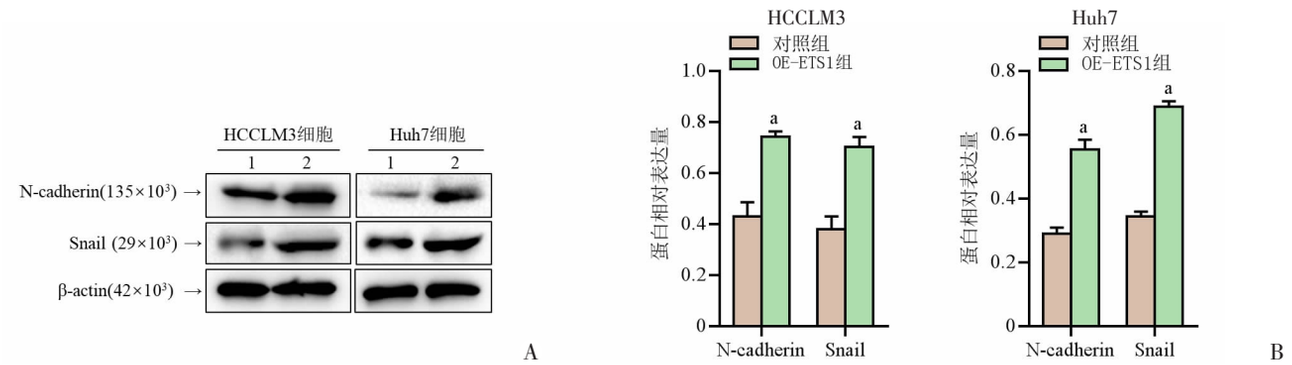
图6　ChIP实验证明ETS1与FBXO45启动子区的结合



a:P<0.001,与对照组比较

A、B:HCCLM3和Huh7细胞中Transwell检测细胞侵袭迁移能力;C、D:统计分析各组侵袭迁移细胞数

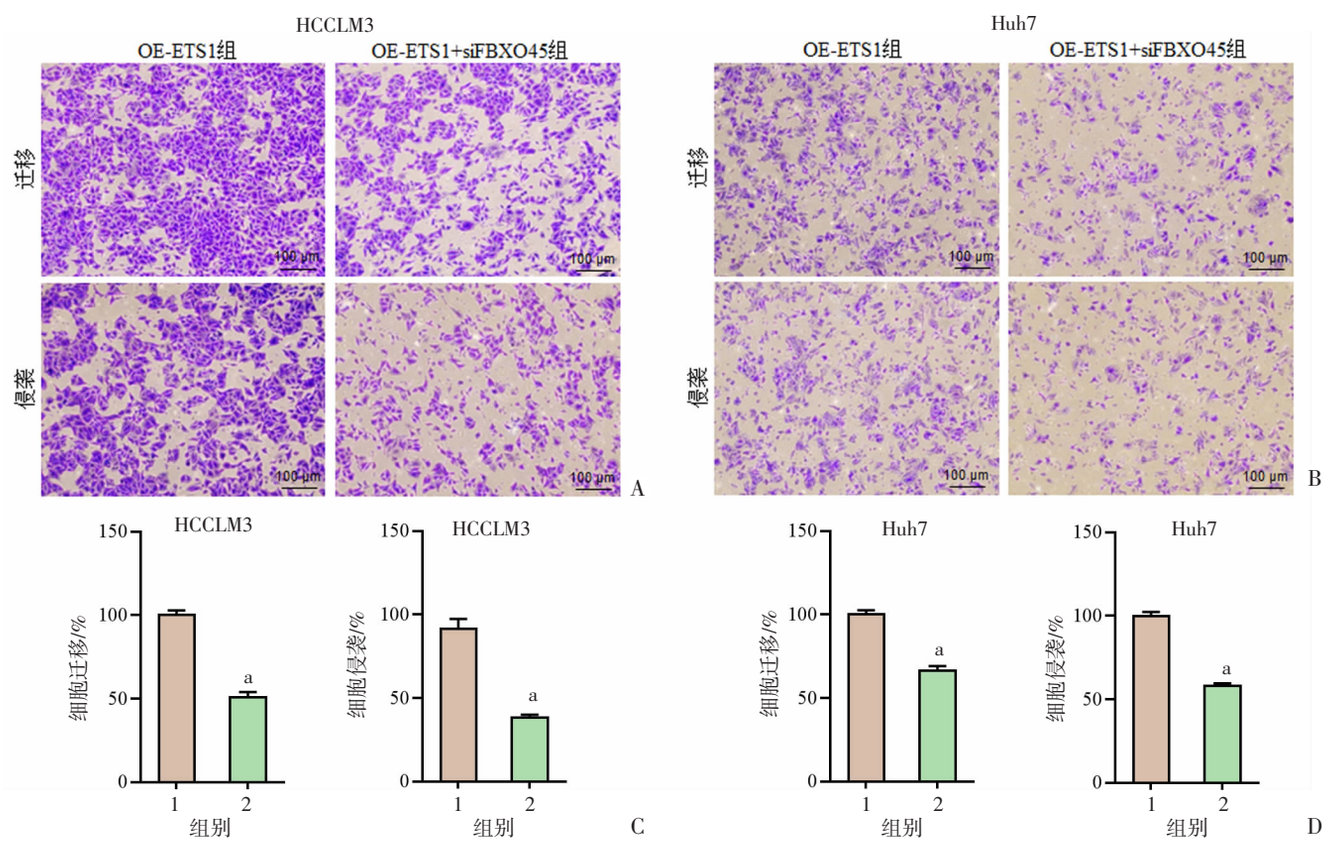
图7　HCCLM3和Huh7中过表达ETS1后检测对迁移侵袭的影响



1:对照组;2:OE-ETS1组; a:$P<0.01$,与对照组比较

A:Western blot检测N-cadherin、Snail蛋白表达水平;B:蛋白表达水平相对定量分析

图8 HCCLM3和Huh7中过表达ETS1后对EMT途径相关蛋白表达水平的影响



1:OE-ETS1组,2:OE-ETS1+siFBXO45组; a:$P<0.01$,与OE-ETS1组比较

A、B:HCCLM3和Huh7细胞中Transwell检测细胞侵袭迁移能力;C、D:统计分析各组侵袭迁移细胞数

图9 HCCLM3和Huh7中过表达ETS1后敲低FBXO45检测对迁移侵袭的影响

3 讨论

肝细胞癌是临床常见的恶性肿瘤,严重危害人类健康[1]。尽管各种各样的治疗带来了一定的疗效,但其复发率高,转移率高导致其预后仍然不容乐观[2]。既往研究数据表明[11],绝大多数肿瘤患者包括肝癌,往往都是由于肿瘤后期的远处转移导致恶病质慢性消耗而死亡。所以研究肝癌转移机制是治疗肝癌很关键的一部分。

ETS1是一种54 kDa的核蛋白,主要作为转录激活剂,同时它也可以抑制基因转录[7-8]。由于它主要在淋巴细胞中表达[5-6],它在免疫中起着关键作用[12-14]。此外,它对血管生理功能也很重要[15-16]。在

许多癌症中,包括乳腺癌、结肠直肠癌、子宫内膜癌、食道癌、胃癌、晚期肝细胞癌和肺癌伴随着较高的ETS1蛋白或RNA表达与较差的肿瘤分化和或侵袭性增加有关[17-24]。既往研究发现ETS1的高表达与乳腺癌和肺癌中促侵袭因子尿激酶型纤溶酶原激活物水平升高相关[25-26],并与口腔癌中基质金属蛋白酶基质分解素-3表达升高也相关[27]。癌细胞中ETS1的高表达也与淋巴结和/或远处转移有关,如结肠直肠癌、胃癌、肺癌、口腔癌和卵巢癌所示[17-18, 22, 26-30]。此外,ETS1表达与宫颈癌、结肠直肠癌、子宫内膜癌、口腔癌和卵巢癌中较高的微血管密度相关,并显示与血管生成血管内皮生长因子、碱性成纤维细胞生长因子和血管生成素-2相关[27, 31-35]。除了癌细胞,癌症基质细胞也可以表达ETS1。在结直肠癌中,内皮细胞ETS1的表达与血管生成刺激因子的表达相关[36],同时较高的基质ETS1表达与结直肠癌发生肺转移相关[37]。因此,在许多癌症中,包括乳腺癌、宫颈癌、结肠直肠癌、胃癌、肺癌、口腔癌和卵巢癌中,ETS1高表达与较差的生存率有关[17-18, 24, 26-28, 38-43]。在肝癌中,ETS1作为下游效应分子在其发生发展中间接参与了部分作用,近些年的大部分研究主要阐述了肝癌治疗中仑伐替尼、索拉非尼和化疗耐药与ETS1密切相关[44-49]。既往研究表明[50],ETS1可促进癌细胞侵袭能力,其主要是由于ETS1和其他ETS家族蛋白通过上调基质金属蛋白酶所驱动的。最近有研究表明[51],ETS1与ZEB2共表达,介导锌脂E盒结合同源框2(Zinc finger E-box-binding homebox 2, ZEB2)诱导的人肿瘤上皮-间充质转化。

既往研究报道了FBXO45异常高表达通过增强IGF2BP1泛素化来促进肝脏肿瘤发生[10],但其高表达原因和在转移中的作用尚不清楚。在本研究中,首先通过网站预测了FBXO45的转录因子,在3个候选的转录因子中发现在敲低ETS1后对FBXO45的表达下调最显著,并通过ChIP实验确定了ETS1为其潜在的转录因子,在TCGA和GEO数据库中进一步发现ETS1表达和FBXO45表达呈正相关,本研究结果显示,ETS1可以转录上调FBXO45表达,同时ETS1在肝癌中能上调EMT途径相关蛋白的表达,这与既往研究报道的结果一致[51],在本研究中,EMT通路的激活促进了肝癌细胞的侵袭转移。在进一步功能实验中证明,敲低FBXO45能显著逆转ETS1所介导的肝癌的侵袭转移。

综上所述,本研究证实了ETS1能通过上调FBXO45而通过激活EMT通路促进肝癌的侵袭和迁移能力,为肝癌转移的治疗提供了部分理论依据。本研究结果不足之处在于未在动物体内以及临床样本中进一步验证,这需要进一步的探索。

利益冲突 本文所有作者声明不存在利益冲突

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(收稿:2025-04-08;修回:2025-05-29)

(编辑 邓强庭)