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· 基础研究 ·

lncRNA TUG1 在儿童肝母细胞瘤中的表达及其与 miR-204 介导的 JAK2-STAT3 通路关系

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摘　要

背景与目的：近年来，儿童肝母细胞瘤（HB）的治疗方面取得一定的进步，但整体临床预后仍然较差，因此探索其发病机制和有效治疗靶点具有重要意义。本研究探讨长链非编码 RNA（lncRNA）牛磺酸上调基因 1（TUG1）与 JAK2-STAT3 通路相关分子在 HB 组织中的表达，初步分析 HB 中 TUG1 与 miR-204 介导的 JAK2-STAT3 血管生成信号通路之间的关系。

方法：选取 2017 年 3 月—2018 年 4 月湖南省儿童医院收治的 60 例 HB 患儿为研究对象，收集所有患儿 HB 肿瘤组织及其远端瘤旁正常组织，分别采用免疫组化与 Western blot 法检测组织中 JAK2、STAT3 及下游血管生成相关分子蛋白的表达，用 qRT-PCR 法检测组织中 TUG1、miR-204 与 JAK2、STAT3 及下游血管生成相关分子的 RNA 表达，并分析 HB 组织中 TUG1 与 miR-204 的表达的相关性。此外，在人 HB 细胞系 HepG2 中，观察 TUG1 敲减或 miR-204 过表达后，JAK2、STAT3 及下游血管生成相关分子的 RNA 表达的变化。

结果：免疫组化结果显示，HB 组织中 JAK2 与 STAT3 蛋白的阳性表达率明显高于瘤旁正常组织（JAK2：40.1% *vs.* 16.9%；STAT3：55.7% *vs.* 19.8%，均 $P<0.05$）。qRT-PCR 结果显示，HB 组织中 TUG1、JAK2、STAT3 及血管生成相关分子 VEGF、VEGFR2、HIF-1α 的 RNA 表达均较瘤旁组织明显上调（均 $P<0.05$）；HB 组织中，TUG1 与 miR-204 的表达呈明显负相关（$r=-0.962$，$P=0.014$）。Western blot 结果显示，HB 组织中 JAK2、STAT3 及下游血管生成相关分子的蛋白表达均较瘤旁组织明显上调（均 $P<0.05$）。HepG2 中，TUG1 敲减或 miR-204 过表达后，JAK2、STAT3 及下游血管生成相关分子的 RNA 与蛋白表达均明显下调（均 $P<0.05$）。

结论：HB 患儿肿瘤组织内 TUG1 的表达上调，并伴有 JAK2-STAT3 通路的活性升高，且 TUG1 与 miR-204 的表达呈负相关，这提示在 HB 中，TUG1 可能通过抑制 miR-204 表达，从而激活 JAK2-STAT3 通路，促进 HB 的血管生成。

关键词　肝肿瘤；肿瘤，生殖细胞和胚胎性；RNA，长链非编码；新生血管化，病理性

中图分类号：R735.7

Expression of lncRNA TUG1 pediatric in hepatoblastoma and its association with miR-204-mediated JAK2-STAT3 pathway

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Abstract

Background and Aims: Although a certain progress has been made in the treatment of hepatoblastoma (HB) in children, the overall clinical prognosis is still poor. So, exploring its pathogenesis and effective therapeutic targets are of great importance. This study was conducted to investigate the expressions of the long non-coding RNA taurine-upregulated gene 1 (TUG1) and the molecules associated with JAK2-STAT3 pathway in HB tissue and preliminarily analyze the relationship between TUG1 and miR-204-mediated JAK2-STAT3 angiogenic signaling pathway.

Methods: Sixty pediatric patients with HB admitted in Hunan Children's Hospital from March 2017 to April 2018 were enrolled as study subjects. The HB tumor tissues along with the tumor-adjacent normal tissues of the patients were collected. The protein expressions of JAK2, STAT3 and their downstream angiogenesis-related molecules in the tissue samples were detected by immunohistochemical staining and Western blot, respectively. The RNA expressions of TUG1 and miR-204 as well as JAK2 and STAT3 and their downstream angiogenesis-related molecules in the tissue samples were determined by qRT-PCR method, and the correlation between TUG1 and miR-204 expressions in HB tissue was analyzed. Moreover, in human HB cell line HepG2, the changes in RNA and protein expression levels of JAK2, STAT3 and their downstream angiogenesis-related molecules were analyzed after TUG1 knockdown or miR-204 overexpression.

Results: The results of immunohistochemical staining showed that the positive expression rates of both JAK2 and STAT3 HB tissue were significantly higher than those in tumor-adjacent normal tissue (JAK2: 40.1% *vs.* 16.9%; STAT3: 55.7% *vs.* 19.8%, both $P<0.05$). The results of qRT-PCR showed that the RNA expression levels of TUG1, miR-204 as well as JAK2 and STAT3 and their downstream angiogenesis-related molecules that included VEGF, VEGFR2 and HIF-1α were significantly up-regulated in HB tissue than those in tumor-adjacent normal tissue (all $P<0.05$), and there was a significant negative correlation between TUG1 and miR-204 expressions in HB tissue ($r=-0.962$, $P=0.014$). The results of Western blot showed that the protein expression levels of JAK2 and STAT3 and their downstream angiogenesis-related molecules were significantly upregulated in HB tissue than those in tumor-adjacent normal tissue (all $P<0.05$). In HepG2 cells after TUG1 knockdown or miR-204 overexpression, the RNA and protein expressions of JAK2 and STAT3 and their downstream angiogenesis-related molecules were significantly down-regulated (all $P<0.05$).

Conclusion: In the tumor tissues from HB children, the expressions of TUG1 is up-regulated, accompanied with the increased activity of JAK2-STAT3 pathway, and there is also a negative correlation between TUG1 and miR-204 expressions. These findings suggest that TUG1 can probably activating the JAK2-STAT3 pathway and thereby promote the angiogenesis through inhibiting miR-204 expression in HB.

Key words Liver Neoplasms; Neoplasms, Germ Cell and Embryonal; RNA, Long Noncoding; Neovascularization, Pathologic

CLC number: R735.7

肝母细胞瘤（hepatoblastoma，HB）是一种来源于肝脏母细胞的胚胎性肿瘤，儿童期最为常见，约占肝脏原发性肿瘤的60%，发病率位于儿科腹部实体肿瘤第3位，且呈逐年上升趋势[1-2]。尽管近年来手术和化疗手段在HB治疗中取得了良好疗效，但由于存在化疗药物的细胞毒性以及手术的高风险性，患者整体临床预后仍然较差[3]。肿瘤侵袭、转移仍是影响HB预后的重要因素，而肿瘤生长与转移是一个依赖于血管的过程，因此，研究HB的血管生成及针对其血管生成的治疗对提高HB的治疗效果、改善预后具有重要意义。

近年来，长链非编码RNA（lncRNA）的表达异常或功能失调与恶性肿瘤的关系备受关注。目前发现，HB组织中有多个调控基因转录的lncRNA表达异常，并且可能在HB的发生发展中起了重要作用。有研究显示，lncRNA TUG1对目标基因的转录、转录后及表观遗传学等多种生物学功能具有调控作用，其异常表达能够参与肺癌、乳腺

癌、肝癌等多种恶性肿瘤的发生发展，提示TUG1作为关键的肿瘤病理学调控分子，有望为肿瘤治疗提供潜在靶点[4-7]。但目前TUG1对HB发生发展的影响及作用机制尚不明确。本研究观察了HB组织中lncRNA牛磺酸上调基因1（TUG1）、血管生成有关的JAK2-STAT3通路信号分子及该通路上游的微小RNA（miRNA）与下游的相关效应分子的表达，并结合细胞实验初步分析它们之间的关系。

1　材料与方法

1.1　实验材料

本研究中60例HB患儿的肿瘤组织及其远端瘤旁正常组织来自湖南省儿童医院手术患者。其中，男25例，女35例；年龄2个月至11岁，平均4.7岁；病理类型：胚胎型7例，互变型12例，混合型41例。研究正式开展前获本院伦理委员会批准。

人肝母细胞瘤HepG2细胞系购自中科院上海细胞库；RPMA-1640培养基和胎牛血清（fetal bovine serum，FBS）购自美国Hyclone公司；0.25%胰蛋白酶、青链霉素混合液和脱脂奶粉购自西安科昊生物公司；Lipofectamine®2000转染试剂购自美国Invitrogen公司；引物、siRNA以及慢病毒过表达载体购自上海吉玛生物公司；qRT-PCR试剂购自Takara生物公司；JAK2-STAT3信号通路蛋白及血管生成相关蛋白VEGF、VEGFR2、HIF-1α和GAPDH抗体分别购自英国Abcam和美国Cell Signaling Technology生物公司；辣根过氧化物酶（HPR）标记的二抗购自武汉博士德生物科技有限公司；ECL化学发光液购自上海碧云天生物科技有限公司。

1.2　实验方法

1.2.1　免疫组化染色方法　将HB组织及其远端瘤旁正常组织样本进行石蜡包埋，切片后采用二甲苯脱蜡以及梯度乙醇水化；随后将切片置于3%甲醇-H_2O_2孵育后转入0.01 mol/L枸橼酸钠盐溶液进行抗原修复；加入5%的胎牛血清室温封闭后分别加入一抗和二抗孵育，采用DAB显色，于显微镜下观察显色情况，并采用中性树胶封片。

1.2.2　细胞培养及转染　采用含10% FBS和1%青链霉素混合液的高糖DMEM培养基，于37 ℃、5%CO_2孵箱中培养HepG2细胞，待细胞处于对数生长期时以6×10^5个/2 mL/孔细胞密度接种于6孔板培养过夜，次日分别转染TUG1抑制物及miR-204模拟物继续培养24 h（qRT-PCR）或48 h（Western blot），检测转染效率。同时，设立转染空质粒细胞为阴性对照组。

1.2.3　qRT-PCR方法　采用TRIzol裂解液提取所获HB组织及其远端瘤旁正常组织样本与HepG2细胞样本的总RNA，并用Epoch紫外分光光度计检测总RNA浓度；随后采用Takara公司5×PrimeScript RT Master Mix反转录试剂盒进行反转录获得总cDNA，以Takara公司2×SYBR Premix Ex Taq II试剂盒实时定量PCR检测上述不同组织及细胞样本中Lnc TUG1、miR-204、JAK2-STAT3信号通路蛋白及血管生成相关蛋白VEGF、VEGFR2、HIF-1α的总RNA表达情况，以GAPDH作为内参基因，qRT-PCR引物序列如表1。

表1　qRT-PCR引物序列

Table 1　Primer sequences for qRT-PCR

基因名称	序列
lncRNA TUG1	
正向	5'-ACC CAT GAA ATC ATC CCC TA-3'
反向	5'-TAG GGG ATG ATT TCATGGGT-3'
miR-204	
正向	5'-TGT GTGTAT GAG CAT GTG TTT G-3'
反向	5'-CAA ACA CAT GCT CAT ACA CAC A-3'
JAK2	
正向	5'-GTG CCA TTT TAC TTT CCT ACC-3'
反向	5'-GGT AGG AAA GTA AAA TGG CAC-3'
STAT3	
正向	5'-GTG CCA TTT TAC TTT CCT ACC-3'
反向	5'-GGT AGG AAA GTA AAA TGG CAC-3'
GAPDH	
正向	5'-GGG GAG AGG ATC CCG GAG AGA-3'
反向	5'-TCT CTC CGG GAT CCT CTC CCC-3'

1.2.4　Western blot方法　采用RIPA裂解液提取HB组织及其远端瘤旁正常组织样本与HepG2细胞样本的总蛋白，并进行BCA蛋白定量；取30 μg蛋白进行SDS-PAGE凝胶电泳及转膜。裁剪目的蛋白条带并采用5%脱脂奶粉溶液室温封闭2 h。分别与适度稀释的JAK2-STAT3信号通路蛋白及血管生成相关蛋白VEGF、VEGFR2、HIF-1α和GAPDH单克隆抗体4 ℃孵育过夜。次日，PBST洗涤目的蛋白条带，加入HRP标记抗人源IgG二抗室温孵育2 h。PBST洗涤3次后进行ECL化学发光检测，并记录蛋白表达量。

1.3　统计学处理

数据处理采用SPSS 17.0统计学软件。计量资

料以均数 ± 标准差（$\bar{x} \pm s$）表示，采用独立样本t检验进行组间对比，相关性分析采用Pearson检验，P<0.05为差异有统计学意义。

2 结 果

2.1 免疫组化结果

免疫组化结果显示，HB肿瘤组织中JAK2和STAT3呈明显阳性表达。JAK2在HB组织及癌旁组织中的阳性表达率分别为40.1%与16.9%，STAT3在HB组织及瘤旁正常组中的阳性表达率分别为55.7%与19.8%，差异均有统计学意义（均P<0.05）（图1）。

2.2 qRT-PCR 结果

qRT-PCR检测结果显示，与远端瘤旁正常组织比较，HB组织中TUG1、JAK2、STAT3及血管生成相关分子VEGF、VEGFR2、HIF-1α的RNA表达明显上调，miR-204明显降低（均P<0.05）。TUG1敲减及miR-204过表达均能明显抑制HepG2细胞中JAK2-STAT3及血管生成相关分子VEGF、VEGFR2、HIF-1α的RNA表达（均P<0.05）（图2）。

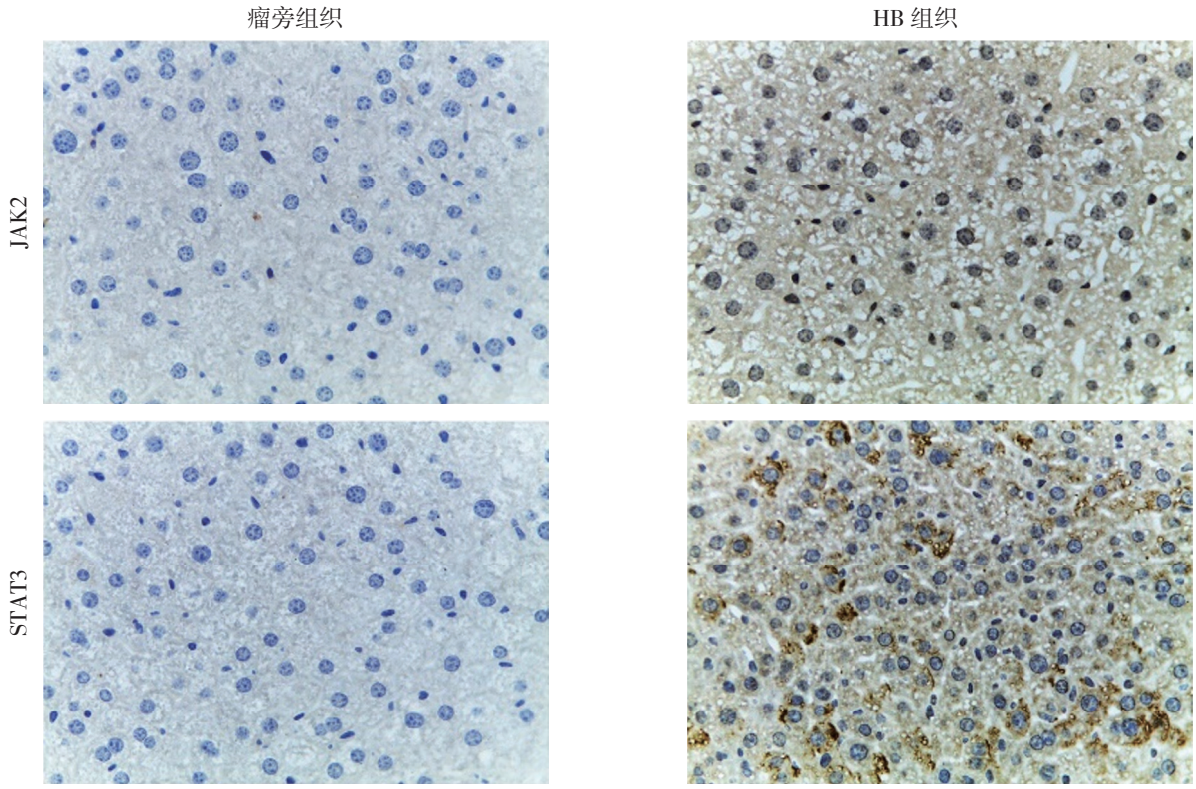

图 1 免疫组化检测 JAK2 与 STAT3 蛋白表达（×100）

Figure 1 Immunohistochemical staining for JAK2 and STAT3 protein expressions (×100)

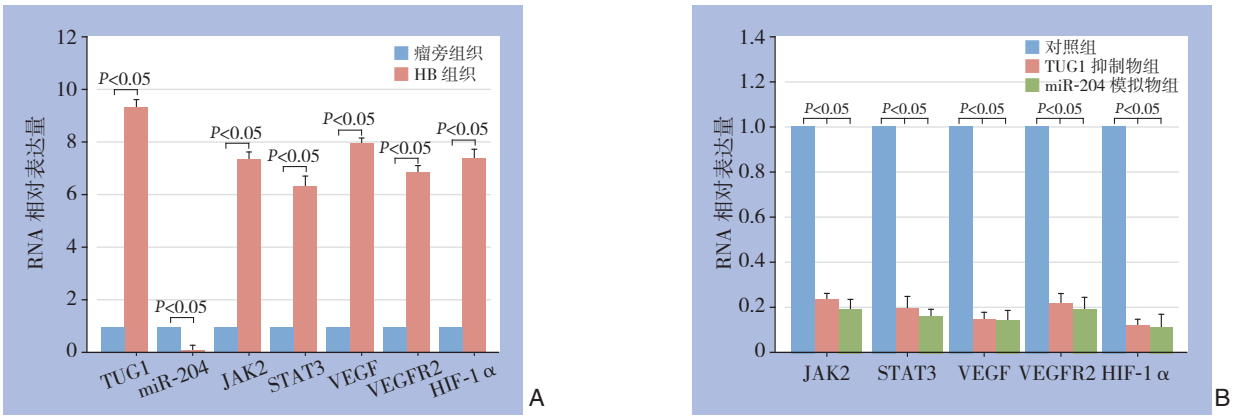

图 2 qRT-PCR 检测结果 A：组织样本；B：HepG2 细胞

Figure 2 Results of qRT-PCR A: Tissue samples; B: HepG2 cells

2.3　TUG1 与 miR-204 在 HB 组织中表达的相关性分析

Pearson相关性分析结果显示，HB患儿肿瘤组织内TUG1与miR-204的表达呈明显负相关（r=−0.962，P=0.014）。

2.4　Western blot 结果

Western blot检测结果示，与远端瘤旁正常组织比较，HB患儿肿瘤组织样本中JAK2-STAT3通路相关分子及血管生成相关分子VEGF、VEGFR2、HIF-1α的蛋白表达明显上调（均P<0.05）。此外，TUG1敲减及miR-204过表达均能够明显抑制HepG2细胞中JAK2-STAT3及血管生成相关分子VEGF、VEGFR2、HIF-1α的蛋白表达（均P<0.05）（图3）。

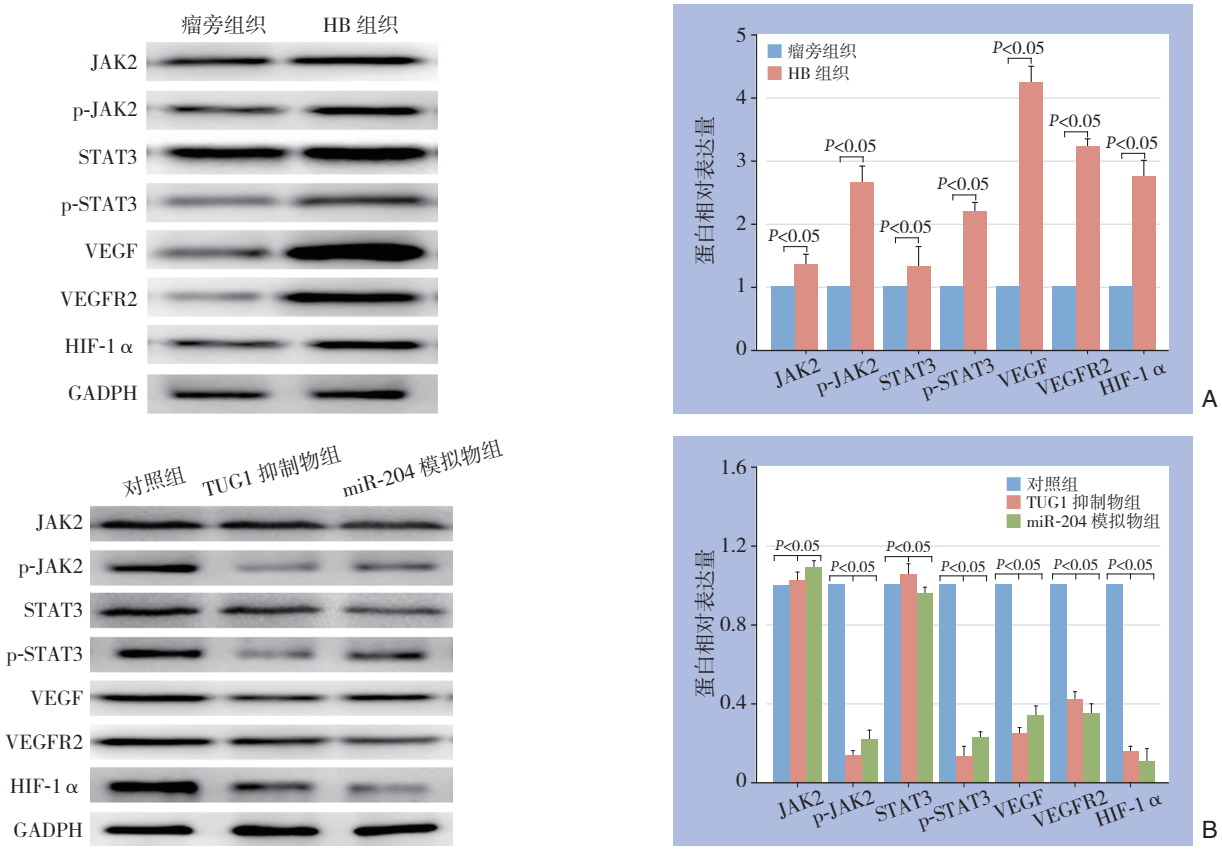

图 3　Western blot 检测结果　A：组织样本；B：HepG2 细胞

Figure 3　Results of Western blot　A: Tissue samples; B: HepG2 cells

3　讨　论

近年来，尽管手术和化疗手段在HB治疗中取得一定疗效，但较高的手术风险和化疗药物的毒性反应仍然制约着HB的临床治疗效果[8-14]。因此，阐明HB的发病机制是改善临床诊疗及防治HB的重要条件。

肿瘤血管的生成过程较为复杂，主要包括血管内皮基质降解、内皮细胞增殖、内皮细胞管道化形成血管环、产生新的基底膜等步骤，肿瘤血管的生成多源于原生血管，并向瘤体不断输送营养成分[15-17]。恶性肿瘤的血管生成过程受血管内皮生成因子VEGF的调节，通过促进血管内皮细胞的增殖进而生成新的血管，充足的营养供给将加速肿瘤的进展。因此，肿瘤血管生成是肿瘤发生发展的重要因素[18]。有学者[19]在HB的临床研究中发现，患儿瘤体中VEGF水平出现差异性高表达，且微血管密度提高，具有较强的新血管生成特征，导致HB生长迅速，易转移复发，预后差等。

通过全基因组分析发现，HB组织中多个调控基因转录的lncRNA表达异常。其中，lncRNA CRNDE可通过调控mTOR信号通路激活靶蛋白发挥抑制HB增殖和血管生成的作用，提示lncRNA可能成为HB的潜在调控因子和预后标志物[20-21]。TUG1属于lncRNA家族重要成员，在多种恶性肿瘤及细胞系如脑胶质瘤、胃癌、食管癌、膀胱癌等肿瘤细胞中异常过表达，进而起到促进肿瘤细胞增殖、转移和抗凋亡的作用。因此，TUG1被认为

是一种原癌基因。此外，蛋白组学研究[22]亦表明TUG1在HB及其转移组织中表达明显上调，上调的TUG1进一步诱导瘤体内异常血管增生，进而增强HB细胞的增殖和侵袭能力，但TUG1在HB发生发展中的作用及其机制还有待深入探究。

miRNA是一类长度约22个核苷酸的非编码RNA，研究表明其能够通过诱导沉默复合体调控转录后靶基因的表达，进而参与细胞的生长、分化、代谢及凋亡等生命过程[23]。而恶性肿瘤的发生发展与原癌基因的过度表达和抑癌基因的沉默相关，在此过程中，JAK2-STAT3信号通路会持续性激活，使下游原癌基因VEGF和MMP-2等过度表达，加速肿瘤的进展[6]。新近研究发现，miR-204可以通过JAK2-STAT3途径减弱肺腺癌中的血管生成，两者存在潜在的结合位点[24-27]。因此，笔者推测JAK2-STAT3可能是TUG1介导miR-204发挥调控HB肿瘤血管生成的重要通路。

本研究通过对2017年3月—2018年4月收集的HB患儿肿瘤组织及其远端瘤旁正常组织中TUG1、miR-204以及JAK2-STAT3的表达进行分析，并通过构建TUG1敲减及miR-204过表达的HepG2细胞系进一步探究TUG1是否通过miR-204介导JAK2-STAT3途径调控肝母细胞瘤血管生成的作用机制，发现HB患儿肿瘤组织较其远端瘤旁正常组织呈现明显病理损伤，且肿瘤组织中JAK2和STAT3呈明显阳性表达。qRT-PCR和Western blot检测结果表明，相比远端瘤旁正常组织，肿瘤组织中TUG1和JAK2-STAT3通路蛋白明显上调；细胞实验结果证实TUG1敲减及miR-204过表达均能够明显抑制HepG2细胞JAK2-STAT3及血管生成相关蛋白VEGF、VEGFR2、HIF-1α的表达。此外，HB患儿肿瘤组织内TUG1和miR-204的表达呈明显负相关（$r=-0.962$，$P=0.014$），提示HB患儿肿瘤组内TUG1的异常表达可能抑制miR-204表达，从而激活JAK2-STAT3途径，促进HB血管生成。揭示TUG1参与调控HB血管生成的作用机制和可用于早期检查和预测病变程度，有望为临床治疗HB提供新分子靶标[28-30]。

综上所述，TUG1/miR-204/JAK2-STAT3信号轴在HB患者血管生成及发生发展进程中可能发挥着重要调控作用，通过靶向TUG1/miR-204/JAK2-STAT3信号轴核心调控分子有望为临床治疗HB提供新的分子靶点和治疗思路。

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