神经生长因子受体p75NTR对肝癌细胞凋亡的影响及其关键功能域

柯小丽[1], 朱倩[2], 田德安[2], 黎培员[2]（1.北京市普仁医院 消化内科，北京 100062；2.华中科技大学同济医学院附属同济医院 消化内科，武汉 430030）

摘要：目的 了解神经生长因子（nerve growth factor，NGF）受体p75NTR在肝癌组织和肝癌细胞株HepG2中的表达，探讨p75NTR对肝癌细胞凋亡的影响及其关键功能域。**方法** 收集2006年9月至2008年4月于华中科技大学同济医学院附属同济医院行手术切除患者的肝癌组织标本及对应的癌旁组织标本共26对，应用免疫组织化学法检测trkA和p75NTR在肝癌组织和癌旁组织中的表达。应用Western blot检测NGF在肝癌细胞株HepG2和人胚胎肝细胞株L02中的表达。p75NTR组通过脂质体将p75NTR质粒转染入HepG2细胞中，空载体组将pcDNA3.1空载体转染HepG2细胞，空白对照组为未处理的HepG2细胞。采用Western blot和免疫荧光法检测各组p75NTR的表达。应用聚合酶链式反应（polymerase chain reaction，PCR）构建p75NTR肿瘤坏死因子2受体相关因子结构域（tumor necrosis factor 2 receptor associated factor domain，TRAF）、突触后密度蛋白结合结构域（postsynaptic density protein domain，PSD）和Ⅱ型死亡结构域（type Ⅱ death domain，T2DD）突变质粒，转染入HepG2细胞中，应用流式细胞术检测细胞凋亡，采用方差分析和LSD-*t*检验比较不同功能域点突变对HepG2细胞凋亡的影响。**结果** 免疫组织化学检测表明TrkA和p75NTR在26对肝癌组织和癌旁组织中均未见明显表达。Western blot结果表明，NGF在HepG2细胞中的相对表达量为0.749 ± 0.302，显著高于L02细胞的0.452 ± 0.290，差异有统计学意义（t = 7.421，P = 0.037）。p75NTR质粒转染入HepG2细胞株后，应用Western blot和免疫荧光进行验证，均可见p75NTR高表达，而空载体组和空白对照组未见明显表达。流式细胞术检测表明，p75NTR组、空载体组和空白对照组细胞凋亡率分别为（25.3 ± 3.6）%、（3.2 ± 0.7）%、（3.0 ± 0.8）%，差异有统计学意义（F = 21.740，P ＜ 0.001），其中p75NTR组显著高于空载体组和空白对照组（t = 25.230、23.156，P均＜ 0.001），空载体组和空白对照组差异无统计学意义（t = 0.417，P = 0.692）。进行p75NTR质粒功能域突变后，空白对照组、空载体组、p75NTR组、TRAF组、T2DD组和PSD组的HepG2细胞凋亡率分别为（3.1% ± 0.8）%、（3.5% ± 0.6）%、（25.8% ± 3.3）%、（24.8% ± 4.1）%、（4.4 ± 0.9）%、（23.4% ± 3.3）%，差异有统计学意义（F = 47.794，P ＜ 0.001），其中T2DD组HepG2细胞凋亡率降至与空载体组一致（t = -0.386，P = 0.708）；而TRAF组和PSD组HepG2细胞凋亡率与p75NTR组接近（t = 0.429、0.987，P = 0.677、0.347）。**结论** p75NTR在肝癌组织及HepG2细胞中无明显表达，过表达p75NTR可促进肝癌细胞的凋亡，提示p75NTR在肝癌细胞中发挥肿瘤抑制因子的作用，T2DD是其关键功能域。

关键词：肝细胞癌；神经生长因子受体；p75NTR；凋亡；功能域

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通讯作者：黎培员 Email: pyli@tjh.tjmu.edu.cn

The pro-apoptosis effect of p75NTR on human hepatocelluar carcinoma cells and its key functional domain

Ke Xiaoli[1], Zhu Qian[2], Tian De'an[2], Li Peiyuan[2] *(1.Division of Gastroenterology, Puren Hospital, Beijing 100062, China; 2.Division of Gastroenterology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China)*

Abstract: Objective To investigate the expression of nerve growth factor (NGF) receptor p75NTR in liver cancer tissues and HepG2 cell line, as well as the effects of p75NTR on the apoptosis of HepG2 cells and its key functional domains. **Methods** A total of 26 pairs of HCC tissues and para-carcerous liver tissues in Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology from September 2006 to April 2008 were collected. The expression of p75NTR in HCC tissues and para-carcerous tissues were examined by immunohistochemistry. The expression of NGF in HepG2 cell line and human embryonic hepatocyte lines L02 were detected by Western blot. The p75NTR plasmid was transfected into HepG2 cells by liposome as p75NTR group, pcDNA3.1 empty vector was transfected into HepG2 cells as empty vector group and untreated HepG2 cells were taken as control group. The expression of p75NTR was detected by Western blot and immunofluorescence assay. The p75NTR point mutation plasmids of tumor necrosis factor 2 receptor associated factor domain (TRAF), postsynaptic density protein domain (PSD), type Ⅱ death domain (T2DD) were constructed by polymerase chain reaction (PCR) and transfected into HepG2 cells, respectively. The apoptosis of HepG2 cells were determined by flow cytometry and the effects of mutations in different functional areas on the apoptosis of HepG2 cells were compared by ANOVA and LSD-*t* test. **Results** Immunohistochemistry showed that there were no obvious expression of p75NTR in 26 pairs of HCC tissues and para-carcerous tissues. Western blot showed that the relative expression of NGF in HepG2 cells was 0.749 ± 0.302, which was significantly higher than that in L02 cells (0.452 ± 0.290), the difference was statistically significant (t = 7.421, P = 0.037). p75NTR protein was overexpressed in HepG2 cells which were transfected with p75NTR plasmid and detected by Western blot and immunofluorescence method while there was no obvious expression in empty vector group and blank control group. Flow cytometry showed that the apoptosis rates of HepG2 cells in p75NTR group, empty vector group and blank control group were (25.3 ± 3.6)%, (3.2 ± 0.7)% and (3.0 ± 0.8)%, respectively, the difference was statistically significant (F = 21.740, P < 0.001). The apoptosis rate of HepG2 cells in p75NTR group was significantly higher than those of empty vector control group and blank control group (t = 25.230, 23.156; all P < 0.001) and there were no significant difference between empty vector group and blank control group (t = 0.417, P = 0.692). After the mutation of p75NTR plasmid functional domain, the apoptosis rates of HepG2 cells in blank control group, empty vector group, p75NTR group, TRAF group, T2DD group and PSD group were (3.1% ± 0.8)%, (3.5% ± 0.6)%, (25.8% ± 3.3)%, (24.8% ± 4.1)%, (4.4 ± 0.9)% and (23.4% ± 3.3)%, respectively, the difference was statistically significant (F = 47.794, P < 0.001). The apoptosis rate of HepG2 cells in T2DD group was close to the empty vector group (t = -0.386, P = 0.708) and the apoptosis rate of HepG2 cells in TARF and PSD group were close to p75NTR group (t = 0.429, 0.987; P = 0.677, 0.347). **Conclusions** There are no obvious expression of p75NTR in HCC tissues and HepG2 cells. Overexpression of p75NTR could promote the apoptosis of HCC cells. It is suggested that p75NTR may be a tumor suppressor in HCC cells and T2DD domain maybe the key functional domain.

Key words: Hepatocellular carcinoma; Nerve growth factor receptor; p75NTR; Apoptosis; Functional domain

原发性肝癌是常见的恶性肿瘤，发病率和病死率分别居全球恶性肿瘤第6位和第3位[1]。全世界每年新发肝癌约80万例，其中一半发生在中国[2]，具体发病机制尚未明确。神经生长因子（nerve growth factor，NGF）是神经营养蛋白家族的一种，其与神经细胞生长、分化、修复和再生有关[3]。NGF还与肿瘤的发生、侵袭和转移有关[4,5]。研究表明，NGF在肝癌组织中高表达，肝癌患者血清NGF水平显著升高，且与肿瘤大小和TNM分级相关[6]。NGF主要通过其受体发挥作用，TrkA（tropomyosin receptor kinase A）是其高亲和性受体，可诱导细胞生长、分化，产生生物学效应[7]。p75NTR（p75 neurotrophin receptor）是其低亲和力受体，p75NTR的作用具有双重性，与TrkA同时存在时，p75NTR可增强NGF与TrkA的结合力，调节TrkA的信号转导，促进细胞增殖；p75NTR单独存在时，与NGF结合发挥促进细胞凋亡的作用[8]。p75NTR在多种恶性肿瘤的生长、侵袭和转移中发挥重要作用[9]，但目前有关p75NTR在肝癌组织和肝癌细胞株中表达的报道较少，其对肝癌细胞的作用和机制也未明确。本研究通过检测p75NTR在肝癌组织和肝癌细胞株中的表达探讨其对肝癌细胞凋亡的影响，并研究其可能发挥作用的关键功能域，以期为肝癌的发病机制和治疗提供研究基础和思路。

1 资料与方法

1.1 肝癌及癌旁组织标本 收集2006年9月至2008年4月于华中科技大学同济医学院附属同济医院行手术切除的肝癌患者组织标本（术后均经病理证实为肝细胞癌）及对应的癌旁组织（距离癌组织边缘约3.0 cm）标本共26对。手术新鲜标本采用液氮冻存和4%甲醛固定分别保存。本研究所有患者均知情同意，通过医院伦理委员会审批（TJ-C20210301）。

1.2 免疫组织化学法检测trkA和p75NTR的表达 取甲醛固定的组织，常规制作石蜡切片，采用免疫组织化学SP法检测肝癌组织和癌旁组织trkA和p75NTR的表达，操作按试剂盒（北京中杉金桥公司）说明进行，抗体为1∶100兔抗人trkA、p75NTR多克隆抗体（美国Santa Cruz公司）。

1.3 细胞培养和质粒转染 肝癌细胞株HepG2、人胚胎肝细胞株L02由本试验室保存，以含10%新生牛血清的DMEM培养基培养。按说明书操作，以Lipofectamine2000（美国Introgen公司）转染质粒。p75NTR组通过脂质体将p75NTR质粒转染入HepG2细胞中，空载体组为将pcDNA3.1空载体转染HepG2细胞，空白对照组为未处理的HepG2细胞。

1.4 Western blot检测细胞株NGF和p75NTR蛋白的表达 HepG2细胞和L02细胞按常规方法提取蛋白，行Western blot检测，每孔上样量为50 μg。一抗采用1∶200兔抗人NGF和p75NTR多克隆抗体（美国Santa Cruz公司），二抗采用1∶2000辣根过氧化物酶标记羊抗兔抗体（立陶宛Fermentas公司）。应用自动凝胶系统检测条带的光密度值。每组试验均重复3次。

1.5 免疫荧光法检测细胞株p75NTR蛋白的表达 将转染的HepG2细胞接种于盖玻片上生长，多聚甲醛固定，10% Trixon处理，1∶200兔抗人p75NTR多克隆抗体（美国Santa Cruz公司）4 ℃孵育18 h，1∶2000罗丹明标记的羊抗兔抗体（美国Santa Cruz公司）避光孵育30 min，甘油封片后于荧光显微镜下观察。

1.6 流式细胞术检测细胞凋亡 转染的HepG2细胞培养48 h后采用胰酶消化，调整细胞浓度至5×10^5/ml，Annexin V-FITC + PI双染色（深圳晶美公司）后上机检测。每组试验均重复3次。

1.7 p75NTR胞内功能域点突变质粒的构建 含人全长p75NTR cDNA的pcDNA3.1-75NTR真核表达质粒由加拿大McGill大学Barker教授惠赠，真核载体质粒pcDNA3.1由本实验室保存。根据p75NTR mRNA及蛋白序列，其胞内段有3个功能域：肿瘤坏死因子2受体相关因子（tumor necrosis factor 2 receptor associated factor，TRAF）结合域同源区，Ⅱ型死亡结构域（type Ⅱ death domain，T2DD），位于C末端的突触后密度蛋白（postsynaptic density protein，PSD）结合结构域。针对3个功能域设计的3对点突变引物见表1。应用3对点突变引物进行PCR，得到点突变的p75NTR序列，插入pcDNA3.1真核表达质粒中，测序证实。

1.8 统计学处理 应用SPSS 17.0统计软件进行数据分析。NGF在HepG2细胞中的相对表达量及细胞凋亡率为计量资料，符合正态分布，以$\bar{x} \pm s$表示，两组间比较采用独立样本t检验，多组间比较采用方差检验，组内两两比较采用LSD-t检验。以$P < 0.05$为差异有统计学意义。

2 结果

2.1 TrkA和p75NTR在肝癌组织和癌旁组织中的表达 免疫组织化学检测表明TrkA和p75NTR蛋白在26对肝癌组织和癌旁组织中均未见明显表达，见图1。

2.2 NGF在HepG2细胞和L02细胞中的表达 Western blot结果表明，NGF在HepG2细胞中的相对表达量为0.749 ± 0.302，显著高于L02细胞的0.452 ± 0.290，差

异有统计学意义（$t=7.421$，$P=0.037$）。见图2。

2.3 p75NTR在HepG2细胞中的表达　HepG2细胞转染pcDNA3.1-75NTR和空载体pcDNA3.1后，采用Western blot检测p75NTR，p75NTR组可见p75NTR显著高表达，而空载体组和空白对照组中均未检测出p75NTR明显表达（图3）。同样，以免疫荧光法检测p75NTR表达，与Western blot结果一致（图4）。

2.4 p75NTR过表达对HepG2细胞凋亡的影响　HepG2细胞转染pcDNA-75NTR和空载体pcDNA3.1后，采用流式细胞仪检测细胞凋亡（图5），p75NTR组、空载体组和空白对照组细胞凋亡率分别为（25.3 ± 3.6）%、（3.2 ± 0.7）%、（3.0 ± 0.8）%，差异有统计学意义（$F=21.740$，$P<0.001$），其中p75NTR组显著高于空载体组和空白对照组（$t=25.230$，23.156，P均<0.001），空载体组和空白对照组差异无统计学意义（$t=0.417$，$P=0.692$）。

2.5 p75NTR蛋白的关键功能域　以PCR法分别点突变p75NTR的3个关键功能域，测序证实：TRAF功能域840位碱基A突变为C，相应赖氨酸突变为天冬酰胺；T2DD功能域1041位碱基G突变为C，相应谷氨酸突变为天冬氨酸；PSD功能域1268位碱基C突变为A，相应丝氨酸突变为酪氨酸。将3种点突变质粒分别转染入HepG2细胞中，采用流式细胞仪检测细胞凋亡。空白对照组、空载体组、p75NTR组、TRAF组、T2DD组、PSD组的凋亡率分别为：（3.1 ± 0.8）%、（3.5 ± 0.6）%、（25.8 ± 3.3）%、（24.8 ± 4.1）%、（4.4 ± 0.9）%、（23.4 ± 3.3）%，6组的凋亡率差异有统计学意义（$F=47.794$，$P<0.001$），其中T2DD组细胞凋亡率降至与空载体组一致（$t=-0.386$，$P=0.708$）；而TRAF组和PSD组细胞凋亡率与p75NTR组接近（$t=0.429$、0.987；$P=0.677$、0.347），见图6。

表 1　针对 TRAF 功能域、T2DD 功能域和 PSD 功能域的 3 对点突变引物序列

名称	引物序列
TRAF功能域	上游：5'-GTGGAACAGCTGCAACCAAAATAAACAAGGC-3'
	下游：5'-GCCTTGTTTATTTTGGTTGCAGCTGTTCCAC-3'
T2DD功能域	上游：5'-GACCAAGCGTGAGGACGTAGAGAAACTGCTC-3'
	下游：5'-GAGCAGTTTCTCTACGTCCTCACGCTTGGTC-3'
PSD功能域	上游：5'-AGTCCACTGCCACATACCCAGTGTGAACTCA-3'
	下游：5'-TGAGTTCACACTGGGTATGTGGCAGTGGACT-3'

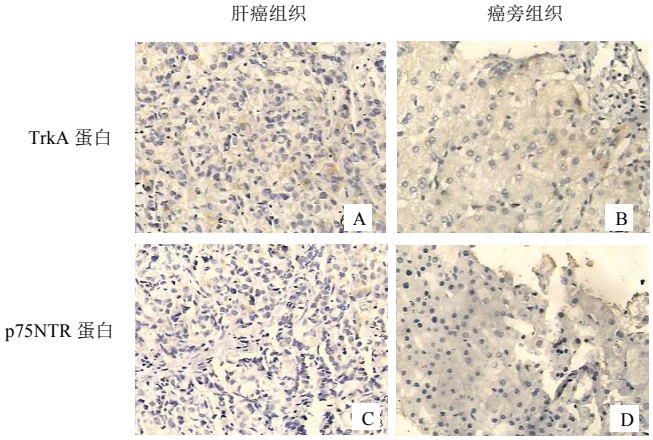

图 1　NGF 受体 TrkA 和 p75NTR 在肝癌组织及癌旁组织中的表达（免疫组织化学 DAB 显色，× 400）

注：A 为免疫组织化学法检测 TrkA 蛋白，肝癌组织未见棕黄色颗粒；B 为免疫组织化学法检测 TrkA 蛋白，癌旁组织未见棕黄色颗粒；C 为免疫组织化学法检测 p75NTR 蛋白，肝癌组织未见棕黄色颗粒；D 为免疫组织化学法检测 p75NTR 蛋白，癌旁组织未见棕黄色颗粒

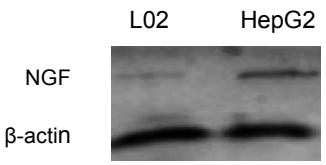

图 2　Western blot 检测 NGF 蛋白在 HepG2 细胞和 L02 细胞中的表达

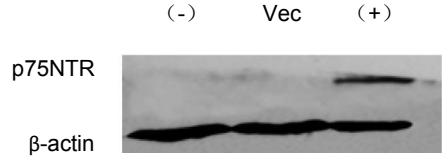

图 3　Western blot 检测 p75NTR 蛋白在 HepG2 细胞中的表达

注：（-）为空白对照；Vec 为空载体组，转染 pcDNA3.1 载体质粒；（+）为 p75NTR 组，转染 pcDNA3.1-p75NTR 质粒

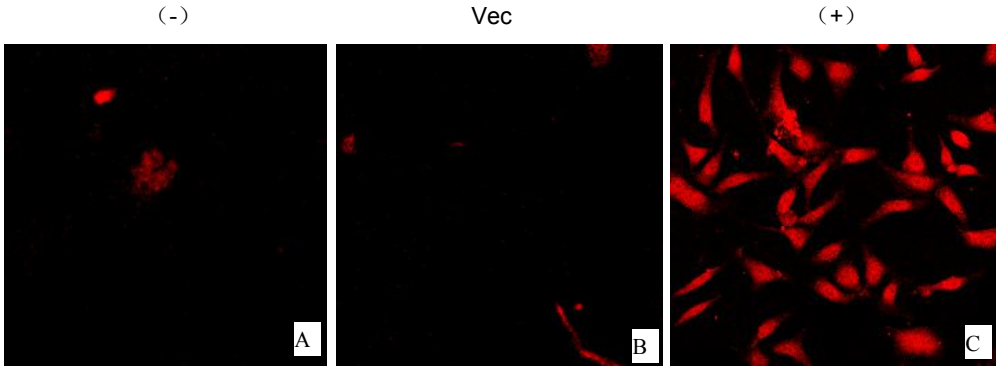

图 4 免疫荧光法检测 p75NTR 蛋白在 HepG2 细胞中的表达

注：A 示空白对照组（-）未见红色荧光；B 示空载体组（Vec）未见红色荧光；C 示 p75NTR 组（+）可见红色荧光，提示 p75NTR 显著表达

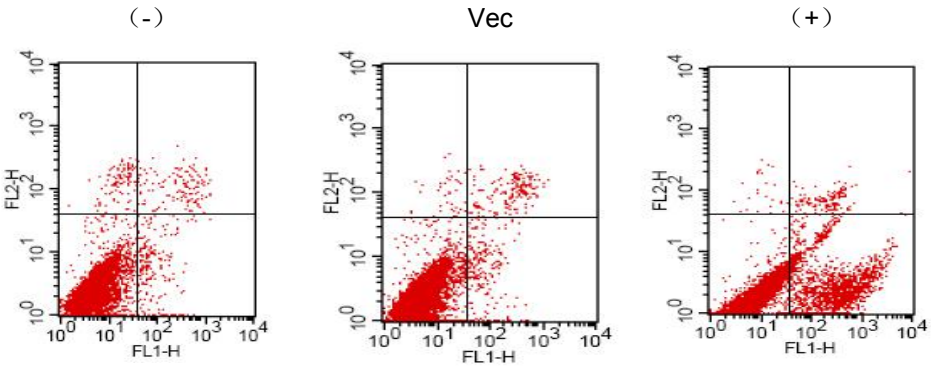

图 5 流式细胞术检测 p75NTR 过表达对 HepG2 细胞凋亡的影响

注：（-）为空白对照；Vec 为空载体组，转染 pcDNA3.1 载体质粒；（+）为 p75NTR 组，转染 pcDNA-p75NTR 载体质粒，其细胞凋亡率显著高于空白对照组和空载体组

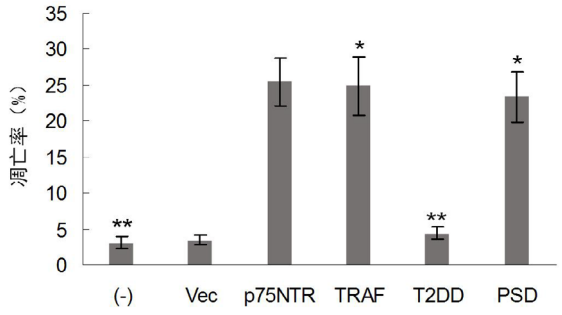

图 6 流式细胞术检测 p75NTR 功能域点突变对 HepG2 细胞凋亡的影响

注：（-）为空白对照组；Vec 为空载体组，转染 pcDNA3.1 载体质粒；p75NTR 为无突变质粒；TRAF 为 TRAF 功能域点突变质粒；T2DD 为 T2DD 功能域点突变质粒；PSD 为 PSD 功能域点突变质粒；* 与 p75NTR 相比 $P > 0.05$；** 与 Vec 相比 $P > 0.05$

3 讨论

过去认为NGF只作用于神经细胞，其与神经细胞的生长和分化有关[10,11]，关于NGF的研究也多与神经系统相关[12]，后来有研究表明NGF与肝癌有关[6]，其他研究也表明，在卵巢癌[13]、宫颈癌[14]、前列腺癌[15]及乳腺癌[16]等肿瘤中，NGF均呈高表达状态，其与肿瘤生长、血管生成和转移等生物学行为有关[9]。本研究表明在肝癌细胞株中NGF的表达显著高于胚胎肝细胞株，这也与组织学研究结果相符。

作为一种生长因子，NGF也主要以自分泌或旁分泌方式通过受体发挥作用。NGF的受体有2种：TrkA和p75NTR。TrkA主要分布于神经系统的效应细胞中，如外周感觉神经元、交感神经元和基底前脑等中枢胆碱能神经元。TrkA是由原癌基因*trk*编

码的一种酪氨酸激酶受体，可与NGF特异性结合，是其高亲和性受体，可激活酪氨酸激酶信号传递系统，从而启动细胞活性，产生生物效应，与调节基因表达和诱导细胞分化有关[17,18]。本研究通过免疫组织化学方法检测了26对肝癌组织和癌旁组织，均未发现有TrkA的明显表达。

p75NTR属糖蛋白受体，为NGF的低亲和力受体，除与NGF结合外，还可与其他神经营养蛋白结合。p75NTR广泛分布于大多数正常组织、胚胎组织及其来源的肿瘤，在施万细胞、少突胶质细胞和运动神经元中也有表达[8,9]。p75NTR的表达与甲状腺癌[19]、乳腺癌[20,21]和胰腺癌[22]等多种肿瘤的发生和预后有关。在胃癌、膀胱癌和前列腺癌等肿瘤中，p75NTR表达减少或缺失[8]。也有研究表明，p75NTR可通过抑制肿瘤细胞的增殖和诱导凋亡而抑制前列腺癌和膀胱癌的生长[23,24]，提示其可能是一种肿瘤抑制因子。本研究在肝癌组织中未检测到TrkA和p75NTR的表达，在肝癌细胞株HepG2中均未检测到p75NTR的明显表达，但肝癌组织和肝癌细胞株中NGF的表达均升高，因此我们设想，如果将p75NTR转入肝癌细胞，是否可引起肝癌细胞株凋亡增多？

体外实验中，将p75NTR转染入胃癌、膀胱癌细胞株过表达，转染后细胞生长受到抑制，细胞周期停滞，进一步提示p75NTR可能为肿瘤抑制因子[9]。那么p75NTR是否对肝癌细胞也发挥抑癌作用？我们将p75NTR真核表达质粒转染入HepG2肝癌细胞株中，发现与空载体对照组相比，p75NTR过表达可显著增加肝癌细胞株的凋亡，提示p75NTR可在肝癌细胞中发挥肿瘤抑制因子的作用，可能成为肝癌的治疗靶点，但需在动物实验中进一步验证。

p75NTR发挥诱导凋亡作用的关键位点和作用机制尚未明确。本研究针对p75NTR胞内段的3个功能域（TRAF功能域、T2DD功能域和PSD功能域）[25]，通过PCR方法设计了关键氨基酸点突变质粒，并将其转染入HepG2细胞中，结果表明TRAF功能域和PSD功能域突变后，仍可引起细胞明显凋亡，与未突变p75NTR一致。而T2DD功能域1041位碱基G突变为C，相应谷氨酸突变为天冬氨酸后，细胞凋亡率与空载体转染类似，提示p75NTR主要通过T2DD功能域发挥促凋亡作用。但后续T2DD功能域通过何种信号转导通路引起肝癌细胞凋亡，仍需进一步研究。

综上，NGF在肝癌组织中高表达，而其受体TrkA和p75NTR在肝癌中无表达。肝癌细胞中转染p75NTR可促进其凋亡，其中T2DD功能域是p75NTR的主要功能域，随着对p75NTR作用及其机制的深入研究，其可能为肝癌治疗提供新思路。

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·读者·作者·编者·

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