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血清 TAP、TFF3 与晚期胃癌患者含奥沙利铂化疗方案敏感性和预后的关系*

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摘要 目的:探讨血清肿瘤异常蛋白(TAP)、三叶因子3(TFF3)与晚期胃癌患者应用含奥沙利铂化疗方案敏感性和预后的关系。**方法:**选择2017年1月至2020年1月河北大学附属医院收治的115例晚期胃癌患者,所有患者接受含奥沙利铂化疗方案治疗,根据疗效分为敏感组(47例)和耐药组(68例)。化疗前检测血清TAP、TFF3水平,受试者工作特征(ROC)曲线分析TAP、TFF3预测晚期胃癌患者接受含奥沙利铂化疗疗效的价值。治疗后随访,Wilcoxon检验不同血清TAP、TFF3表达下晚期胃癌患者中位OS时间差异。**结果:**耐药组血清TAP、TFF3水平高于敏感组($P<0.05$)。TAP、TFF3预测晚期胃癌患者含奥沙利铂化疗耐药的曲线下面积分别为0.717、0.690,联合TAP和TFF3预测晚期胃癌患者含奥沙利铂化疗耐药的曲线下面积为0.801,高于单独TAP、TFF3单独检测。随访期间失访2例,死亡54例,高水平TAP、高水平TFF3晚期胃癌患者中位OS时间短于低水平TAP、低水平TFF3晚期胃癌患者($P<0.05$)。**结论:**对含奥沙利铂化疗耐药的晚期胃癌患者血清TAP、TFF3水平显著增高,高水平TAP、TFF3晚期胃癌患者中位OS时间较短,联合检测血清TAP和TFF3可预测晚期胃癌患者化疗反应性和预后。

关键词:晚期胃癌;奥沙利铂;化疗;TAP;TFF3;敏感性;预后

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Relationship between Serum TAP, TFF3 and Sensitivity of Containing Oxaliplatin Chemotherapy Regimen and Prognosis in Patients with Advanced Gastric Cancer*

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ABSTRACT Objective: To explore the relationship between serum tumor abnormal protein (TAP), trefoil factor 3 (TFF3) and the sensitivity and prognosis of containing oxaliplatin chemotherapy regimen in patients with advanced gastric cancer. **Methods:** 115 patients with advanced gastric cancer who were admitted to Affiliated Hospital of Hebei University from January 2017 to January 2020 were selected. All patients received containing oxaliplatin chemotherapy regimen treatment, and they were divided into sensitive group (47 cases) and drug-resistant group (68 cases) according to the efficacy. Serum TAP and TFF3 levels were detected before chemotherapy, and the value of TAP and TFF3 in predicting the efficacy of oxaliplatin chemotherapy in patients with advanced gastric cancer was analyzed by receiver operating characteristic (ROC) curve. After treatment of follow-up, Wilcoxon analysis was used to analyze the difference in the median OS survival time of patients with advanced gastric cancer with different serum TAP and TFF3 expression. **Results:** Serum TAP and TFF3 levels in the drug-resistant group were higher than those in the sensitive group ($P<0.05$). TAP and TFF3 predicted the area under curve of containing oxaliplatin chemotherapy resistance of patients with advanced gastric cancer were 0.717 and 0.690, respectively, combined TAP and TFF3 predicted the area under curve of containing oxaliplatin chemotherapy resistance of patients with advanced gastric cancer was 0.801, which was higher than TAP and TFF3 alone detection. During follow-up, 2 cases were lost to follow-up, and 54 cases died, the median OS survival time of patients with high level of TAP and high level of TFF3 and advanced gastric cancer were lower than those of patients with low level of TAP and low level of TFF3 and advanced gastric cancer ($P<0.05$). **Conclusion:** Serum TAP and TFF3 levels were significantly higher in advanced gastric cancer patients who were resistant to containing oxaliplatin chemotherapy, and high levels of TAP and TFF3 were associated with a shorter median OS survival time in advanced gastric cancer patients, and the com-

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bined detection of serum TAP and TFF3 may predict chemotherapeutic responsiveness and prognosis in advanced gastric cancer patients.

Key words: Advanced gastric cancer; Oxaliplatin; Chemotherapy; TAP; TFF3; Sensitivity; Prognosis

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前言

胃癌是世界上常见的恶性肿瘤之一,早期胃癌通过根治性手术切除可获得较好的生存获益,但是早期胃癌缺乏特异性征象,检出率较低,多数患者确诊即为晚期,晚期胃癌往往失去手术切除机会,以内科治疗为主,预后较差^[1,2]。奥沙利铂是第三代铂类抗肿瘤药物,通过阻止脱氧核糖核酸(DNA)复制和转录促使癌细胞凋亡,含奥沙利铂的化疗方案用于一线治疗晚期或转移性胃癌,被证实可提高客观缓解率,延长中位生存时间^[3,4]。化疗耐药导致的肿瘤进展,是晚期胃癌的主要挑战^[5,6]。肿瘤异常蛋白(TAP)是异常糖蛋白、钙组蛋白和细胞癌变后基因表达的常见物质的复合物,当肿瘤生长到一定程度时,TAP大量排入血液中,引起血清TAP水平增高,因此TAP常被作为肿瘤诊断和预后预测的标志物^[7,8]。三叶因子3(TFF3)是一种分泌蛋白,通过与特定受体结合促进肿瘤细胞的增殖、侵袭和转移,并抑制癌细胞凋亡,在肿瘤发生、发展中发挥着重要作用^[9,10]。本研究拟探讨血清TAP、TFF3与晚期胃癌患者含奥沙利铂化疗方案敏感性和预后的关系,旨在为临床治疗和预后预测提供参考。

1 资料与方法

1.1 临床资料

选择2017年1月至2020年1月河北大学附属医院收治的115例晚期胃癌患者,纳入标准:①经组织病理活检证实为胃腺癌,且人类表皮生长因子受体2(HER2)阴性^[11];②TNM分期Ⅳ期;③美国东部肿瘤协作组(ECOG)评分≤2分,可接受含奥沙利铂化疗,既往未接受任何形式的抗肿瘤治疗;④年龄在18岁以上,80岁以下。排除标准:①可手术切除患者;②同时发生其他部位肿瘤的患者;③不具有可用于影像学评估的可测量病灶;④合并严重肝肾功能衰竭;⑤临床资料缺失。男72例、女43例;年龄41~78岁,平均(63.07±11.22)岁;病理类型:腺癌79例,印戒细胞癌36例;中分化腺癌37例,高分化腺癌24例,高分化腺癌18例。Lauren分型:弥漫型47例,肠型68例;远处转移69例。本研究已经获得河北大学附属医院伦理委员会批准,患者及其家属均知情同意并签署同意书。

1.2 方法

1.2.1 血清TAP、TFF3检测 所有患者化疗前采集静脉血约3 mL注入干燥试管,室温静置后待血液凝固,取上层液于离心

管(相对离心力3260×g,时间10 min)离心,取上清液-80℃保存待检。采用Sunrise全自动酶标仪(瑞士帝肯公司)应用酶联免疫吸附试验检测血清TFF3水平,TFF3试剂盒购自美国BioLegend公司。采集静脉血2 mL均匀推在载玻片上,长度超过玻片长度的2/3,平放待干,18℃~25℃放置10 min,取TAP试剂在血片上滴三滴,每滴50 μL,形成10~12 mm/φ的斑点,干燥2 h,采用TAP图像分析仪以及TAP试剂盒(浙江瑞生医疗科技有限公司)检测凝聚物面积即TAP水平。

1.2.2 化疗方案 含奥沙利铂化疗:第1 d,奥沙利铂(赛诺菲(杭州)制药有限公司,国药准字H20064296)130 mg/m²静滴2 h;第1-14 d卡培他滨(齐鲁制药有限公司,国药准字H20133361)1000 mg/m²口服,21 d为1个化疗周期,给药直至患者病情恶化或出现无法耐受的副作用。所有患者均接受至少2个周期的化疗。

1.3 疗效评估及分组

参考RECIST1.1实体瘤疗效判断标准^[12]评估化疗疗效,完全缓解(CR):所有病灶全部消失,且至少维持4周;部分缓解(PR):较基线病灶最大径之和缩小≥30%,且至少维持4周;疾病进展(PD):基线病灶最大径之和增加>20%或有新的病灶出现;疾病稳定(SD):介于PR和PD之间。以CR+PR为敏感,SD+PD为耐药。根据化疗反应将患者分为敏感组和耐药组。

1.4 随访

所有患者出院后定期门诊复查随访1年,每3-6个月1次。统计随访期间患者总生存(OS)情况,OS时间定义为病理确诊到死亡时间。

1.5 统计学分析

SPSS 25.00分析数据,计量资料符合正态分布以($\bar{x} \pm s$)表示采用独立样本t检验。受试者工作特征曲线(ROC)分析TAP、TFF3预测晚期胃癌患者对含奥沙利铂化疗的反应性。Wilcoxon检验不同血清TAP、TFF3水平晚期胃癌患者中位OS时间差异。检验水准 $\alpha=0.05$ 。

2 结果

2.1 敏感组和耐药组血清TAP、TFF3比较

化疗过程中有68例出现耐药,根据化疗反应将患者分为敏感组(47例)和耐药组(68例)。耐药组血清TAP、TFF3水平高于敏感组($P<0.05$),见表1。

表1 敏感组和耐药组血清TAP、TFF3比较($\bar{x} \pm s$)

Table 1 Comparison of serum TAP and TFF3 between sensitive group and drug-resistant group($\bar{x} \pm s$)

Groups	n	TAP(μm^2)	TFF3($\mu\text{g/L}$)
Drug-resistant group	68	173.65±39.15	35.26±6.19
Sensitive group	47	140.32±25.08	19.35±4.21
t		5.148	15.330
P		0.000	0.000

2.2 血清 TAP、TFF3 预测晚期胃癌患者含奥沙利铂化疗耐药的价值分析

TAP、TFF3 预测晚期胃癌患者含奥沙利铂化疗耐药的曲

线下面积分别为 0.717、0.690，联合 TAP 和 TFF3 预测晚期胃癌患者含奥沙利铂化疗耐药的曲线下面积为 0.801，高于单独 TAP、TFF3，见表 2 和图 1。

表 2 血清 TAP、TFF3 预测晚期胃癌患者含奥沙利铂化疗耐药的价值分析

Table 2 Value analysis of serum TAP and TFF3 in predicting containing oxaliplatin chemotherapy resistance of patients with advanced gastric cancer

Indexes	Area under curve(95%CI)	Critical value	Sensitivity	Specificity	Youden index
TAP	0.717(0.626~0.797)	156.92 μm^2	72.06	72.34	0.444
TFF3	0.690(0.579~0.773)	27.03 $\mu\text{g/L}$	73.53	68.09	0.416
Unite	0.801(0.727~0.842)	-	89.71	70.34	0.621

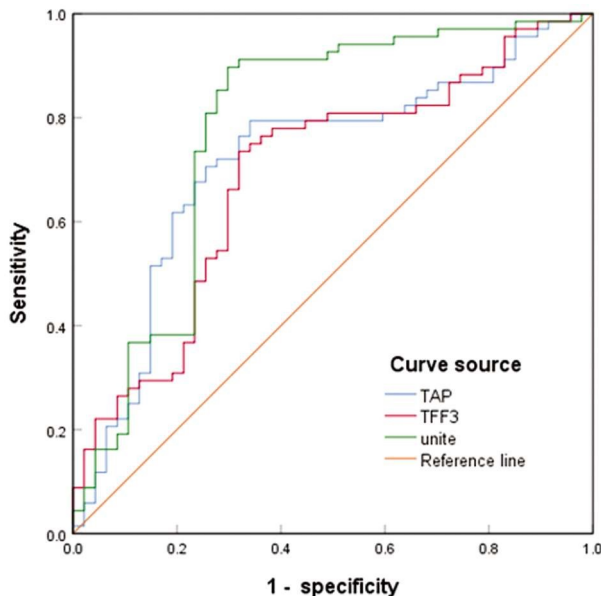


图 1 血清 TAP、TFF3 预测晚期胃癌患者含奥沙利铂化疗耐药的 ROC 图

Fig.1 ROC chart of serum TAP and TFF3 predicting containing oxaliplatin chemotherapy resistance of patients with advanced gastric cancer

2.3 不同血清 TAP、TFF3 表达晚期胃癌患者生存分析

随访期间失访 2 例，死亡 54 例。高水平 TAP ($\text{TAP} \geq 160.03 \mu\text{m}^2$, 58 例)、高水平 TFF3 ($\text{TFF3} \geq 228.76 \mu\text{g/L}$, 57 例) 晚期胃癌患者中位 OS 生存时间分别为 3.13(1~6)个月, 3.67(1~7)个月, 低于低水平 TAP ($\text{TAP} < 160.03 \mu\text{m}^2$, 55 例)、低水平 TFF3 ($\text{TFF3} < 228.76 \mu\text{g/L}$, 56 例) 晚期胃癌患者的 7.05(2~10)个月, 8.04(2~11)个月 ($Z=11.521, 12.861, P < 0.05$)。

3 讨论

胃癌是导致恶性肿瘤相关死亡的第四大原因, 晚期胃癌多伴转移性病灶, 预后较差, 细胞毒化疗和放射治疗仍然是晚期胃癌全身治疗的最主要方法^[13,14]。以铂为基础的化疗是不可手术切除的晚期胃癌患者治疗的主要手段, 含奥沙利铂化疗具有较高的疗效和安全性, 优于其他含铂方案(比如顺铂), 可显著提高生存率和控制局部复发^[15], 但是有多数患者不可避免对奥沙利铂化疗耐药, 通常导致化疗失败和疾病进展^[16]。因此探讨与晚期胃癌含奥沙利铂的化疗结果相关的标志物, 对改善临床治疗方案和患者预后有着重要的意义。

研究表明异常糖链糖蛋白的发生与肿瘤密切相关, 恶性肿瘤患者体内可检测到多种糖链糖蛋白异常表达, 包括甲胎蛋白、癌胚抗原、碳水化合物抗原等 20 多种异常糖链结构蛋白^[17,18]。TAP 是异常糖链糖蛋白的复合物, 因细胞中癌基因和抑癌基因发生基因突变后产生, 血液中 TAP 的含量随着肿瘤的发生和发展而增加, 因此 TAP 可间接反映癌细胞的数量和恶性程度^[19,20]。TAP 作为肿瘤的广谱筛查标志物, 已被证实可在胃癌诊断和术后复发转移评估^[21]、直肠癌化疗反应评估^[22]、晚期非小细胞肺癌抗程序性死亡受体 1 治疗疗效评估^[23]中具有较高的参考价值。本研究发现晚期胃癌患者血清 TAP 水平增高与含奥沙利铂化疗耐药有关, 高水平 TAP 晚期胃癌患者中位生存时间短于低水平 TAP 患者, 表明 TAP 与晚期胃癌对含奥沙利铂化疗耐药以及预后有关。分析原因为肿瘤细胞恶性增殖、侵袭过程中伴随糖蛋白基因的突变, 进而导致外周血中 TAP 水平增高^[24], 经含奥沙利铂化疗前高血清 TAP 水平, 表明肿瘤细胞处于持续恶性增殖状态, 因此治疗后容易出现化疗耐药, 因此 TAP 水平越高, 患者出现耐药的风险越大, 预后不良风险更高。

TFF3 属于三叶因子家族, 在黏液分泌上皮细胞中表达和分泌, 通过与黏蛋白的相互作用和刺激细胞运动参与保护和维持上皮细胞分泌功能, TFF3 表达异常与肿瘤发生和进展有关^[25,26]。研究显示 TFF3 高表达通过激活上皮-间充质转化过程, 诱导 Twist1、蜗牛蛋白和波形蛋白表达升高, 降低上皮性钙黏附素表达促进结肠癌细胞增殖、迁移和侵袭^[27], TFF3 在胃癌中高表达, 且与胃癌的发生、浸润、转移和预后有关^[28]。TFF3 与肿瘤细胞对化疗耐药也有关, 研究表明通过上调 TFF3 可促使乳腺癌细胞对紫杉醇和阿霉素耐药^[29], TFF3 通过激活蛋白激酶 B 及其下游靶基因编码的 B 细胞淋巴瘤/白血病-2 蛋白, 促使肝细胞癌对化疗耐药^[30]。本研究发现 TFF3 与晚期胃癌患者对含奥沙利铂化疗耐药有关, 耐药组血清 TFF3 水平高于敏感组, 高水平 TFF3 晚期胃癌患者中位 OS 时间短于低水平 TFF3 患者。分析原因为晚期胃癌细胞发生和进展过程中 TFF3 高表达可介导血管内皮生长因子表达, 促使新生血管形成和胃癌进展^[31], 化疗前高水平 TFF3 导致新生血管形成和癌细胞加速增殖, 降低化疗杀伤力, 进而表现为耐药, 引起生存率低下。

ROC 分析显示 TAP、TFF3 在预测晚期胃癌化疗反应方面具有一定价值, 联合两项指标后预测效能明显提高, 表明联合检测血清 TAP、TFF3 水平有助于临床对含奥沙利铂化疗疗效的评估和预判, 对指导临床治疗有着重要意义。

综上, 经含奥沙利铂化疗后耐药的晚期胃癌患者血清 TAP、TFF3 水平均增高, 高水平 TAP、TFF3 晚期胃癌患者中位 OS 时间短于低水平 TAP、TFF3 患者, 联合检测血清 TAP、TFF3 水平有助于评估晚期胃癌患者化疗反应性以及预后。

参考文献(References)

- [1] Smyth EC, Nilsson M, Grabsch HI, et al. Gastric cancer [J]. Lancet, 2020, 396(10251): 635-648
- [2] Patel TH, Cecchini M. Targeted Therapies in Advanced Gastric Cancer [J]. Curr Treat Options Oncol, 2020, 21(9): 70
- [3] Yu J, Gao Y, Chen L, et al. Effect of S-1 Plus Oxaliplatin Compared With Fluorouracil, Leucovorin Plus Oxaliplatin as Perioperative Chemotherapy for Locally Advanced, Resectable Gastric Cancer: A Randomized Clinical Trial [J]. JAMA Netw Open, 2022, 5 (2): e220426
- [4] Wang X, Li S, Sun Y, et al. The protocol of a prospective, multicenter, randomized, controlled phase III study evaluating different cycles of oxaliplatin combined with S-1 (SOX) as neoadjuvant chemotherapy for patients with locally advanced gastric cancer: RESONANCE-II trial[J]. BMC Cancer, 2021, 21(1): 20
- [5] Marin JJ, Al-Abdulla R, Lozano E, et al. Mechanisms of Resistance to Chemotherapy in Gastric Cancer [J]. Anticancer Agents Med Chem, 2016, 16(3): 318-334
- [6] Chen Z, Li Y, Tan B, et al. Progress and current status of molecule-targeted therapy and drug resistance in gastric cancer [J]. Drugs Today (Barc), 2020, 56(7): 469-482
- [7] Zhang L, Guo X, Min Y, et al. Tumor abnormal protein (TAP) examination contributes to primary diagnosis of bladder cancer[J]. Int J Clin Exp Med, 2015, 8(10): 18528-18532
- [8] Cheng Y, Fang Q, Chen Y, et al. High Expression of Tumor Abnormal Protein Preoperatively Predicts Poor Prognosis of Patients With Esophageal Squamous Cell Carcinoma [J]. Front Surg, 2021, 8(2): 609719
- [9] Cui HY, Wang SJ, Song F, et al. CD147 receptor is essential for TFF3-mediated signaling regulating colorectal cancer progression[J]. Signal Transduct Target Ther, 2021, 6(1): 268
- [10] Wang X, Qin H. TFF3 promotes pituitary tumor cell migration and angiogenesis via VEGFA [J]. Acta Neurobiol Exp (Wars), 2022, 82 (2): 237-243
- [11] Ajani JA, Bentrem DJ, Besh S, et al. Gastric cancer, version 2.2013: featured updates to the NCCN Guidelines [J]. J Natl Compr Canc Netw, 2013, 11(5): 531-546
- [12] Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1)[J]. Eur J Cancer, 2009, 45(2): 228-247
- [13] Machlowska J, Baj J, Sitarz M, et al. Gastric Cancer: Epidemiology, Risk Factors, Classification, Genomic Characteristics and Treatment Strategies[J]. Int J Mol Sci, 2020, 21(11): 4012
- [14] Song Z, Wu Y, Yang J, et al. Progress in the treatment of advanced gastric cancer[J]. Tumour Biol, 2017, 39(7): 1010428317714626
- [15] Liu P, Chen J, Zhao L, et al. PD-1 blockade synergizes with oxaliplatin-based, but not cisplatin-based, chemotherapy of gastric cancer[J]. Oncoimmunology, 2022, 11(1): 2093518
- [16] Wang J, Sun Y, Zhang X, et al. Oxidative stress activates NORAD expression by H3K27ac and promotes oxaliplatin resistance in gastric cancer by enhancing autophagy flux via targeting the miR-433-3p[J]. Cell Death Dis, 2021, 12(1): 90
- [17] 祁洁, 邹士涛, 李晓庆. 肿瘤异常糖链糖蛋白在乳腺癌中的表达及其临床意义[J]. 中华内分泌外科杂志, 2019, 13(2): 103-106
- [18] 杨丹, 刘永萍. 肿瘤异常蛋白检测在食管癌放疗近期疗效评价中的价值[J]. 医学临床研究, 2017, 34(12): 2448-2450
- [19] Liu Z, Cai J, Yu Y, et al. Tumor Abnormal Protein as a Novel Biomarker in Papillary Thyroid Carcinoma[J]. Clin Lab, 2017, 63(3): 479-485
- [20] Meng J, Li W, Zhang M, et al. An update meta-analysis and systematic review of TAP polymorphisms as potential biomarkers for judging cancer risk[J]. Pathol Res Pract, 2018, 214(10): 1556-1563
- [21] 毛智军, 王建华, 宋斌, 等. 胃癌患者血清肿瘤异常蛋白检测的临床意义[J]. 陕西医学杂志, 2017, 46(7): 976-978
- [22] 王锋, 马进, 王少敏. 血清中肿瘤异常蛋白 / 异常糖链糖蛋白在直肠癌治疗前后的表达观察 [J]. 结直肠肛门外科, 2016, 22(2): 150-153
- [23] 杨冬, 辛勇, 陈辰, 等. 血清 TAP、PDCD-5、TNF- α 与晚期非小细胞肺癌患者抗 PD-1 治疗疗效的关系分析 [J]. 现代生物医学进展, 2022, 22(14): 2737-2742
- [24] 胡颖燕, 任冰洁, 李大鹏, 等. 肿瘤异常糖链糖蛋白在卵巢癌中的诊断效能评估[J]. 广西医科大学学报, 2020, 37(12): 2205-2209
- [25] May FE, Westley BR. TFF3 is a valuable predictive biomarker of endocrine response in metastatic breast cancer [J]. Endocr Relat Cancer, 2015, 22(3): 465-479
- [26] Morito K, Nakamura J, Kitajima Y, et al. The value of trefoil factor 3 expression in predicting the long-term outcome and early recurrence of colorectal cancer[J]. Int J Oncol, 2015, 46(2): 563-568
- [27] Yusufu A, Shayimu P, Tuerdi R, et al. TFF3 and TFF1 expression levels are elevated in colorectal cancer and promote the malignant behavior of colon cancer by activating the EMT process [J]. Int J Oncol, 2019, 55(4): 789-804
- [28] 范立凤, 刘慧敏. TFF3 和 VEGF 表达与胃癌发生、浸润和转移的相关性[J]. 肿瘤学杂志, 2017, 23(2): 125-129
- [29] Wu H, Gu J, Zhou D, et al. LINC00160 mediated paclitaxel-And doxorubicin-resistance in breast cancer cells by regulating TFF3 via transcription factor C/EBP β [J]. J Cell Mol Med, 2020, 24 (15): 8589-8602
- [30] You ML, Chen YJ, Chong QY, et al. Trefoil factor 3 mediation of oncogenicity and chemoresistance in hepatocellular carcinoma is AKT-BCL-2 dependent[J]. Oncotarget, 2017, 8(24): 39323-39344
- [31] Guleng B, Han J, Yang JQ, et al. TFF3 mediated induction of VEGF via hypoxia in human gastric cancer SGC-7901 cells [J]. Mol Biol Rep, 2012, 39(4): 4127-4134