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HGF 和 EZH2 在宫颈癌组织中的表达及其与临床病理特征的关系 *

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摘要 目的:探讨肝细胞生长因子(HGF)、果蝇 zeste 基因增强子 2(EZH2)在宫颈癌组织中的表达及其与临床病理特征的关系。**方法:**选取 2016 年 10 月到 2018 年 1 月期间在新疆医科大学附属肿瘤医院接受治疗的宫颈癌患者 50 例,收集其手术切除的病理组织作为宫颈癌组的检测标本,另选取同期在我院收治的子宫肌瘤患者,收集其行全子宫切除术时切除的宫颈组织,其中上皮内瘤样病变(CIN)组织和正常宫颈组织各 50 例,CIN 组织作为 CIN 组的检测标本,正常宫颈组织作为对照组的检测标本。比较宫颈癌组、CIN 组和对照组标本中 HGF 和 EZH2 的阳性表达情况。分析 HGF 和 EZH2 的表达与宫颈癌患者临床病理特征的关系,分析宫颈癌组织中 HGF、EZH2 表达的相关性。**结果:**各组标本中的 HGF 和 EZH2 的阳性表达率整体比较差异均有统计学意义($P<0.05$),宫颈癌组、CIN 组的 HGF 和 EZH2 的阳性表达率均明显高于对照组,且宫颈癌组 EZH2 的阳性表达率高于 CIN 组($P<0.05$)。宫颈癌组织中 HGF 和 EZH2 的表达与年龄、肿瘤类型、肿瘤大小无关($P>0.05$),临床分期 II 期、有淋巴结转移、病理分级 G3 的宫颈癌组织中 HGF 和 EZH2 的阳性表达率高于临床分期 I 期、无淋巴结转移、病理分级 G1+G2 的宫颈癌组织($P<0.05$)。经 Spearman 相关分析显示,宫颈癌组织中 HGF 与 EZH2 表达呈正相关($P<0.05$)。**结论:**HGF 和 EZH2 在宫颈癌组织中呈高表达,且其表达水平与临床分期、淋巴结转移、病理分级有关。

关键词:宫颈癌;肝细胞生长因子;果蝇 zeste 基因增强子 2;表达;临床病理特征;关系

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Expression of HGF and EZH2 in Cervical Cancer and Its Relationship with Clinicopathological Characteristics*

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ABSTRACT Objective: To investigate the expression of hepatocyte growth factor (HGF) and enhancer of zeste homolog 2 (EZH2) in cervical cancer and its relationship with the clinicopathological features. **Methods:** 50 cases of cervical cancer who were treated in Cancer Hospital Affiliated to Xinjiang Medical University from October 2016 to January 2018 were selected, the pathological tissue of surgical resection was collected as the specimen of cervical cancer group, another uterine fibroids patients in our hospital during the same period were selected, the cervical tissues removed during hysterectomy were collected, there were 50 cases of intraepithelial neoplasia (CIN) or normal cervical tissue, CIN tissue as a test specimen of CIN group, normal cervical tissue as a test specimen of the control group. The positive expression of HGF and EZH2 in cervical cancer group, CIN group and control group were compared, the relationship between the expression of HGF and EZH2 and clinicopathological characteristics of cervical cancer patients were analyzed, the correlation between the expression of HGF and EZH2 in cervical cancer tissues was analyzed. **Results:** The positive expressions of HGF and EZH2 in all the groups were significantly different ($P<0.05$). The positive expression of HGF and EZH2 in the cervical cancer group and CIN group were significantly higher than that in the control group, the positive expression of EZH2 in the cervical cancer group was significantly higher than that of the CIN group ($P<0.05$). The expression of HGF and EZH2 in cervical cancer was not related to age, tumor type and size of tumor ($P>0.05$). The positive expression rate of HGF and EZH2 in cervical cancer tissues of clinical stage II stage, lymph node metastasis and pathological grade G3 was higher than that of I stage, no lymph node metastasis and pathological grading G1+G2 in cervical cancer tissues ($P<0.05$). Spearman correlation analysis showed that there was a positive correlation between HGF and EZH2 expression in cervical cancer tissues ($P<0.05$). **Conclusion:** HGF and EZH2 are highly expressed in cervical cancer tissues, and their expression level is related to clinical stage, lymph node metastasis and pathological grading.

Key words: Cervical cancer; Hepatocyte growth factor; Enhancer of zeste homolog 2; Expression; Clinicopathological features; Relationship

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前言

宫颈癌是常见的妇科肿瘤,具有较高的发病率和死亡率^[1,2]。高危型人乳头瘤状病毒持续感染是引发宫颈癌的重要原因,近年来随着宫颈细胞学筛查的普遍应用,导致部分宫颈病变可以尽早查出,进而进行针对性的治疗,使得宫颈癌的发病率和死亡率有所下降^[3,4]。肿瘤细胞侵袭和转移仍是导致宫颈癌患者死亡的重要原因,肝细胞生长因子(Hepatocyte growth factor, HGF)是一种多肽生长因子,可促进原代培养的肝细胞生长^[5,6],近年来研究发现^[7,8],HGF在多种恶性肿瘤中异常表达,具有诱导血管生成、促进有丝分裂的作用,进而促进肿瘤细胞发生侵袭和转移,推动恶性肿瘤的进展。果蝇 *zeste* 基因增强子 2 (enhancer of *zeste* homolog 2, EZH2) 是多梳基因 PcG 家族的一员,其具有调控细胞增殖的作用^[9],并且有研究发现^[10,11],EZH2 参与了乳腺癌、胃癌等恶性肿瘤的侵袭和转移,与恶性肿瘤的发生、发展密切相关。目前对 HGF 和 EZH2 在宫颈癌发生、发展中的作用知之甚少,本研究旨在探讨 HGF 和 EZH2 在宫颈癌组织中的表达及其与临床病理特征的关系,以为临床诊断和靶向治疗宫颈癌提供参考,现将研究结果整理报道如下。

1 资料与方法

1.1 一般资料

选取 2016 年 10 月到 2018 年 1 月期间在新疆医科大学附属医院肿瘤医院接受治疗的宫颈癌患者 50 例,收集其手术切除的病理组织作为宫颈癌组的检测标本,纳入标准:(1)所有患者均经临床病理确诊为宫颈癌;(2)术前未接受放疗和化疗者;(3)病历资料完整者;(4)患者及其家属对本研究知情同意,并签署知情同意书。排除标准:(1)合并有其他恶性肿瘤者;(2)合并有严重肝、肾功能障碍者;(3)存在免疫系统疾病者;(4)处于妊娠期和哺乳期者。50 例宫颈癌患者中,鳞癌 40 例,腺癌 10 例,年龄 23-69 岁,平均(48.69±12.04)岁,临床分期:I 期 28 例,II 期 22 例,肿瘤大小:<4 cm 33 例,≥4 cm 17 例,淋巴结转移:有 21 例,无 29 例,病理分级:G1+G2 31 例,G3 19 例。另选取同期在我院收治的子宫肌瘤患者,收集其行全子宫切除术时切除的宫颈组织,其中上皮内瘤样病变(Cervical Intraepithelial Neoplasia, CIN)组织和正常宫颈组织各 50 例,CIN 组织作为 CIN 组的检测标本,正常宫颈组织作为对照组的检测标本。CIN 组年龄 25-68 岁,平均(49.63±12.34)岁,对照组年龄 24-70 岁,平均(50.23±11.67)岁。三组患者的年龄比较无统计学差异($P>0.05$)。本研究符合我院伦理委员会制定的相关规定,并已获得委

员会批准。

1.2 检测方法

所有标本在切除后进行固定、石蜡包埋、切片。采用免疫组化法检测标本中 HGF 和 EZH2 的表达情况,脱蜡前先置于恒温烤箱中加热 20 min,温度为 60℃,采用二甲苯溶液脱蜡,梯度酒精水化。加入枸橼酸钠缓冲溶液,高压锅加热,进行抗原热修复。滴加 3%的过氧化氢甲醇溶液,静置 10 min。山羊血清封闭,室温下湿盒孵育 20 min,甩去多余液体,滤纸吸干。滴加一抗(HGF 多克隆抗体,北京博奥森生物技术有限公司;EZH2 多克隆抗体,北京中山生物技术有限公司),4℃过夜,PBS 缓冲液冲洗 5 min,重复 3 次。滴加生物素二抗,室温孵育 30 min,PBS 缓冲液冲洗 5 min,重复 3 次。DAB 试剂盒(北京中山生物技术有限公司)显色,镜下观察,适时终止反应,苏木精复染,蒸馏水冲洗。采用梯度酒精脱水,二甲苯溶液透明,中性树脂封片。

1.3 结果判读

高倍镜(400×)下进行观察,HGF 主要染色部位为细胞浆,少数在细胞膜和细胞核,EZH2 主要染色部位为细胞核。采用半定量积分法分析标本中 HGF 和 EZH2 的阳性染色情况,镜下随机选取 5 个视野,根据染色强度和阳性细胞率来综合评估。染色强度评分标准:无色得 0 分,淡黄色得 1 分,棕黄色得 2 分,棕褐色得 3 分。阳性细胞率评分标准:阳性细胞率≤25%得 0 分,25%<阳性细胞率≤50%得 1 分,50%<阳性细胞率≤75%得 2 分,阳性细胞率>75%得 3 分。染色强度评分和阳性细胞率评分的乘积≤3 分为阴性,>3 分为阳性。

1.4 观察指标

比较宫颈癌组、CIN 组和对对照组标本中 HGF 和 EZH2 的阳性表达情况。分析 HGF 和 EZH2 的表达与宫颈癌患者临床病理特征的关系,分析宫颈癌组织中 HGF、EZH2 表达的相关性。

1.5 统计学方法

采用 SPSS21.0 进行统计分析,计量资料采用($\bar{x} \pm s$)进行描述,采用 t 检验,计数资料采用率(%)描述,采用 χ^2 检验,采用 Spearman 进行相关性分析, $P<0.05$ 表示差异有统计学意义。

2 结果

2.1 各组标本中 HGF 和 EZH2 的阳性表达情况

各组标本中的 HGF 和 EZH2 的阳性表达率整体比较差异均有统计学意义($P<0.05$),宫颈癌组、CIN 组的 HGF 和 EZH2 的阳性表达率均明显高于对照组,且宫颈癌组 EZH2 的阳性表达率高于 CIN 组($P<0.05$),见表 1。

表 1 各组标本中 HGF 和 EZH2 的阳性表达情况[n(%)]
Table 1 The positive expression of HGF and EZH2 in each group[n(%)]

Groups	n	HGF		EZH2	
		Positive	Negative	Positive	Negative
Cervical cancer group	50	38(76.00) [#]	12(24.00)	36(72.00) ^{**}	14(28.00)
CIN group	50	34(68.00) [#]	16(32.00)	25(50.00) [#]	25(50.00)
Control group	50	8(16.00)	42(84.00)	5(10.00)	45(90.00)
χ^2		42.643		40.097	
P		0.000		0.000	

Note: compared with the control group, [#] $P<0.05$; compared with the CIN group, ^{*} $P<0.05$.

2.2 宫颈癌组织中 HGF 和 EZH2 的表达与临床病理特征的关系

宫颈癌组织中 HGF 和 EZH2 的表达与年龄、肿瘤类型、肿瘤大小无关($P>0.05$),临床分期 II 期、有淋巴结转移、病理分级

G3 的宫颈癌组织中 HGF 和 EZH2 的阳性表达率高于临床分期 I 期、无淋巴结转移、病理分级 G1+G2 的宫颈癌组织($P<0.05$),见表 2。

表 2 宫颈癌组织中 HGF 和 EZH2 的表达与临床病理特征的关系

Table 2 The relationship between the expression of HGF and EZH2 and clinicopathological characteristics in cervical cancer tissues

Clinicopathological characteristics		n	HGF		x ²	P	EZH2		x ²	P
		Positive	Negative	Positive			Negative			
Age	<50 year	28	19(67.86)	9(32.14)	2.313	0.128	19(67.86)	9(32.14)	0.542	0.462
	≥ 50 year	22	19(86.36)	3(13.64)			17(77.27)	5(22.73)		
Tumor type	Squamous cell carcinoma	40	32(80.00)	8(20.00)	1.754	0.185	30(75.00)	10(25.00)	0.893	0.345
	Adenocarcinoma	10	6(60.00)	4(40.00)			6(60.00)	4(40.00)		
Clinical stages	I stage	28	18(64.29)	10(35.71)	4.786	0.029	17(60.71)	11(39.29)	4.020	0.045
	II stage	22	20(90.91)	2(9.09)			19(86.36)	3(13.64)		
Tumor size	<4 cm	33	24(72.73)	9(27.27)	0.164	0.685	23(69.70)	10(30.30)	0.030	0.863
	≥ 4 cm	17	14(82.35)	3(17.65)			13(76.47)	4(23.53)		
Lymph node metastasis	Yse	21	19(90.48)	2(9.52)	4.160	0.041	19(90.48)	2(9.52)	6.131	0.013
	No	29	19(65.52)	10(34.48)			17(58.62)	12(41.38)		
Pathological grading	G1+G2	31	20(64.52)	11(35.48)	4.358	0.037	19(61.29)	12(38.71)	4.641	0.031
	G3	19	18(94.74)	1(5.26)			17(89.47)	2(10.53)		

2.3 宫颈癌组织中 HGF 与 EZH2 表达的相关性分析

经 Spearman 相关分析显示, 宫颈癌组织中 HGF 与 EZH2 表达呈正相关($r=0.410$, $P=0.002$)。

3 讨论

宫颈癌的发病机制较为复杂,是一个涉及到多因素、多阶段的作用的过程,至今尚未完全阐明^[12,13]。宫颈癌患者在发病早期无明显症状,少数患者表现为接触性出血,容易被忽视,在晚期可出现尿频、尿急、便秘、下肢肿痛等继发性症状,并且进行治疗难度大,患者预后较差^[14-16]。肿瘤细胞的侵袭和转移是患者复发和死亡的重要原因,因此探讨与肿瘤细胞侵袭和转移相关的因子具有重要的临床意义。肿瘤细胞的侵袭、转移与细胞增殖能力、新生血管、转移的信号传导等多种因素有关,HGF 和 EZH2 是近年来研究较多的与肿瘤侵袭、转移密切相关的因子^[17-19]。其中 HGF 可通过与其特异性受体 c-Met 结合发挥多重生物作用,在正常情况下,HGF 与 c-Met 短暂结合具有修复损伤组织、促进胚胎发育等作用,然而在肿瘤组织中,HGF 和 c-Met 均呈高表达,可促进肿瘤细胞增殖,并且还可以促进细胞外基质降解、诱导血管生成,为肿瘤细胞的转移、生长提供有利条件,进而促进恶性肿瘤的发生、发展^[20-22]。庄晓萃等人的研究显示^[23],HGF 的表达与乳腺癌的临床分期、淋巴结转移相关。付英等人的研究显示^[24],HGF 的表达与大肠癌患者预后密切相关。EZH2 是表观遗传调控因子多梳抑制复合体 2 的催化亚基,可对细胞周期、细胞分化、细胞衰老等进行调控,其高表达可促进肿瘤细胞增殖,进而促进肿瘤细胞扩散^[25-27]。Geng J 等人的研究显示^[28],EZH2 可通过 VEGF-A/Akt 信号通路促进肺癌的侵袭和转移。李杰宝等人认为^[29,30]EZH2 可作为乳腺癌患者的预后指标。

在本次研究中,宫颈癌组、CIN 组的 HGF 和 EZH2 的阳性表达率均明显高于对照组,且宫颈癌组 EZH2 的阳性表达率高

于 CIN 组($P<0.05$),这说明 HGF 和 EZH2 在宫颈癌组织中呈高表达,提示二者可能参与了宫颈癌的发生和发展。进一步研究显示,临床分期 II 期、有淋巴结转移、病理分级 G3 的宫颈癌组织中 HGF 和 EZH2 的阳性表达明显高于临床分期 I 期、无淋巴结转移、病理分级 G1+G2 的宫颈癌组织($P<0.05$),这说明 HGF 和 EZH2 的表达水平与宫颈癌的进展密切相关,这可能与 HGF 和 EZH2 均可促进肿瘤细胞侵袭、转移有关。相关性分析显示,宫颈癌组织中 HGF 与 EZH2 表达呈正相关($P<0.05$),提示二者的表达可能存在一定的联系,可互相作用共同影响宫颈癌的进展,临床上可通过检测宫颈癌组织中 HGF 和 EZH2 的表达来预测患者的病情发展趋势和预后。然而其具体的机制还有待进一步探讨。

综上所述,HGF 和 EZH2 在宫颈癌组织中呈高表达,且其表达水平与临床分期、淋巴结转移、病理分级有关。本研究初步证明了 HGF 和 EZH2 与宫颈癌的发生、发展密切相关,提示两指标可作为宫颈癌患者的预后的预判指标,然而本研究选取病例数较少,HGF 和 EZH2 与宫颈癌的关系还有待更大样本量的研究进行验证。

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