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HSP70、eIF4E、DNMT1 在宫颈癌中的表达及意义 *

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摘要 目的:探讨热休克蛋白 70(HSP70)、真核细胞翻译起始因子 4E(eIF4E)、DNA 甲基转移酶 1(DNMT1)在宫颈癌中的表达及意义。**方法:**选择 2015 年 2 月至 2017 年 2 月我院接诊的 40 例女性宫颈癌患者为本研究对象,收集所有患者手术切除病理组织制作石蜡切片,并选择我院同期接受其他手术的 35 例标本作为对照组,使用 SP 免疫组织化学法观察乳腺癌组织中 HSP70、eIF4E、DNMT1 染色结果,并分析其与临床病理因素之间的关系。**结果:**在免疫组化结果中显示,40 例宫颈癌组织中,HSP70 阳性表达率为 65.00%(26/40),eIF4E 阳性表达率为 67.50%(27/40),DNMT1 阳性表达率为 72.50%(29/40),均显著高于对照组($P<0.05$);在宫颈癌组织中,HSP70、eIF4E、DNMT1 和分化程度、临床分期及淋巴转移均有密切关系,($P<0.05$);将分化程度、临床分期、淋巴转移、HSP70、eIF4E、DNMT1 进行相关分析,结果显示,HSP70、eIF4E、DNMT1 和分化程度、临床分期及淋巴转移之间均呈正相关($P<0.05$),且 HSP70 和 eIF4E、DNMT1 均呈正相关($P<0.05$),eIF4E 和 DNMT1 呈正相关($P<0.05$)。**结论:**在宫颈癌组织中 HSP70、eIF4E、DNMT1 的高表达和临床病理之间存在密切关系。

关键词:宫颈癌;热休克蛋白 70;真核细胞翻译起始因子 4E;DNA 甲基转移酶 1

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Expression and Significance of HSP70, eIF4E and DNMT1 in Cervical Cancer *

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ABSTRACT Objective: To study Expression and significance of Heat shock protein 70 (HSP70), eukaryotic translation initiation factor 4E (eIF4E), DNA methyltransferase 1 (DNMT1) in cervical cancer. **Methods:** 40 female cervical cancer patients admitted to our hospital from February 2015 to February 2017 were selected as the subjects of this study, all patients were collected for the preparation of paraffin sections after surgical resection of pathological tissues, and 35 specimens received other surgeries in our hospital were selected as the control group. The staining results of HSP70, eIF4E and DNMT1 in breast cancer tissues were observed using SP immunohistochemical method, and the relationship between them and clinicopathological factors was analyzed. **Results:** According to the results of immunohistochemistry, the positive expression rate of HSP70 was 65.00% (26/40), eIF4E was 67.50% (27/40), and DNMT1 was 72.50% (29/40), all significantly higher than the control group ($P<0.05$). In cervical cancer tissues, HSP70, eIF4E, DNMT1 were closely correlated with the degree of differentiation, clinical stage and lymphatic metastasis ($P<0.05$). The correlation analysis of differentiation degree, clinical stage, lymphatic metastasis, HSP70, eIF4E and DNMT1 showed that there was a positive correlation between HSP70, eIF4E, DNMT1 and differentiation degree, clinical stage and lymphatic metastasis ($P<0.05$), and there was a positive correlation between HSP70, eIF4E and DNMT1 ($P<0.05$), and there was a positive correlation between eIF4E and DNMT1 ($P<0.05$). **Conclusion:** There is a close relationship between the high expression of HSP70, eIF4E and DNMT1 in cervical cancer tissues and the clinicopathology, which can promote the disease progression, and this study also provides a new idea for the targeted drug treatment of cervical cancer.

Key words: Cervical cancer; Heat shock protein 70; Eukaryotic cell translation initiation factor 4E; DNA methyltransferase 1

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前言

宫颈癌在妇科中十分常见,发病率居女性恶性肿瘤第二

位,通常发生在 20~55 岁,部分地区还出现了宫颈癌患病的 " 年轻化 " 趋势,早期无明显症状,随着病情的发展可表现为阴道流血、阴道排液等症状,严重影响患者的生活质量^[1,2]。近年

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来,我国进行了宫颈癌筛查工作,使得癌前病变得以早期发现和治疗,大大降低了宫颈癌的发病率和死亡率,但是其晚期复发率和死亡率仍然较高,因此,寻找与宫颈癌发生、侵袭、转移的相关因子,对临床救治具有重要的作用^[3]。有研究显示,在发生宫颈癌时,患者 HSP70、eIF4E、DNMT1 有着明显变化^[4]。HSP70 在细胞中广泛存在,是一种重要生理功能的蛋白质分子,可通过与癌基因、抑癌基因及其产物相互作用,调节细胞增殖^[5]。eIF4E 是一种帽结合蛋白,促进细胞增殖和诱导细胞转化、肿瘤形成和转移^[6]。DNMT1 是一种维持性的甲基化酶,其可以抑制基因转录,促进肿瘤发生^[7]。HSP70、eIF4E、DNMT1 在宫颈癌中表达异常,可能参与了疾病的发展,但其具体意义还需进一步探讨。本研究通过对宫颈癌患者的 HSP70、eIF4E、DNMT1 水平观察与分析,探讨其变化情况及其意义,现报告如下。

1 资料与方法

1.1 一般资料

选择 2015 年 2 月至 2017 年 2 月于我院进行治疗的 40 例宫颈癌患者,所有患者术前均未进行过化疗、放疗,并具有石蜡标本。年龄 32~65 岁,平均(51.73±5.06)岁,其中腺癌 12 例,鳞癌 14 例,鳞腺癌 14 例,此研究已获得我院伦理委员会批准实施,所有患者均知情同意此研究。

纳入标准^[8]:(1)符合宫颈癌临床诊断标准;(2)术后病理组织证实确诊为宫颈癌;(3)未发现远处脏器和组织病灶转移;

(4)认知功能无障碍。排除标准:(1)处于妊娠期和哺乳期者;(2)过敏体质或对治疗药物过敏者;(3)严重脏器官疾病者;(4)不能配合本次研究样品采集者。

1.2 方法

收集所有患者手术切除组织,10%福尔马林固定,常规包埋后 4 μm 连续切片,SP 免疫化学法观察染色结果,试剂盒购于北京中杉金桥生物技术有限公司。

结果判断标准^[9]:细胞无染色 0 分,浅棕色 1 分,弱阳性,棕色 2 分,中阳性,深棕色 3 分,强阳性;阳性细胞所占百分比,<10%为 0 分,10%~30%为 1 分,31%~60%为 2 分,>60%为 3 分;相加两项结果,总分>2 为阳性,反之为阴性。

1.3 统计学分析

以 SPSS18.0 软件包处理,计量资料用均数±标准差($\bar{x} \pm s$)表示,t 检验,计数资料 χ^2 检验,相关性分析使用 Spearman 相关系数, $P<0.05$ 表示差异具有统计学意义。

2 结果

2.1 两组患者 HSP70、eIF4E、DNMT1 阳性率表达比较

在免疫组化学法结果中显示,40 例宫颈癌组织中,HSP70 阳性表达率为 65.00%(26/40),eIF4E 阳性表达率为 67.50%(27/40),DNMT1 阳性表达率为 72.50%(29/40),均显著高于对照组($P<0.05$),见表 1,图 1~图 3。

表 1 两组患者 HSP70、eIF4E、DNMT1 阳性率表达比较[n(%)]

Table 1 Comparison of the positive rates of HSP70, eIF4E and DNMT1 between the two groups[n(%)]

Groups	n	HSP70	eIF4E	DNMT1
Observation group	40	26(65.00)	27(67.50)	29(72.50)
Control group	35	5(14.29)	2(5.71)	3(8.57)
χ^2 value		19.799	30.048	31.186
P value		0.000	0.000	0.000

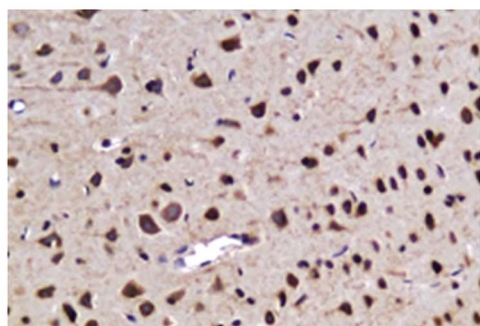


图 1 HSP70 的阳性表达

Fig.1 The positive expression of HSP70

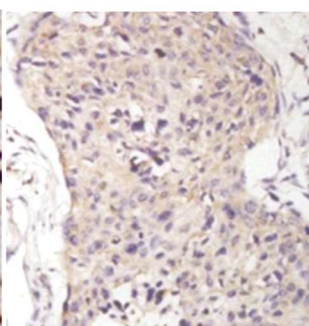


图 2 eIF4E 的阳性表达

Fig.2 Positive expression of eIF4E

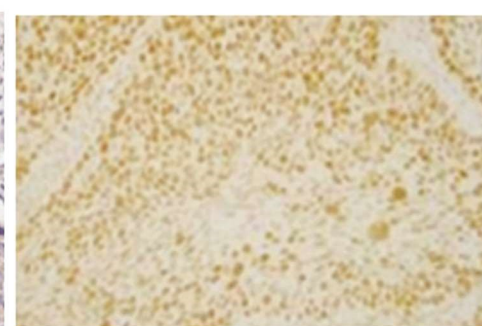


图 3 DNMT1 的阳性表达

Fig.3 Positive expression of DNMT1

2.2 HSP70、eIF4E、DNMT1 阳性表达与宫颈癌临床病理之间的关系

在宫颈癌组织中,HSP70、eIF4E、DNMT1 和分化程度、临床分期及淋巴转移均有密切关系($P<0.05$),见表 2。

2.3 宫颈癌组织中 HSP70、eIF4E、DNMT1 表达和临床病理因素的相关性分析

将上表中具有统计学意义的作为因变量,将 HSP70、

eIF4E、DNMT1 分别作为自变量,在相关性分析结果中显示,HSP70、eIF4E、DNMT1 和分化程度、临床分期及淋巴转移之间均呈正相关($P<0.05$),见表 3。

2.4 HSP70、eIF4E、DNMT1 之间相关性分析

经 Spearman 相关分析显示,HSP70 和 eIF4E、DNMT1 均呈正相关($r=0.428, 0.479, P<0.01$),eIF4E 和 DNMT1 呈正相关($r=0.513, P<0.01$)。

表 2 HSP70、eIF4E、DNMT1 阳性表达与宫颈癌临床病理之间的关系

Table 2 Relationship between positive expression of HSP70, eIF4E and DNMT1 and clinicopathological features of cervical cancer

Clinicopathology		n	HSP70				eIF4E			DNMT1		
			Positive rate	χ^2	<i>P</i>		Positive rate	χ^2	<i>P</i>	Positive rate	χ^2	<i>P</i>
Age	≥ 45	21	14	0.054	0.816		14	0.014	0.906	16	0.302	0.583
	<45	19					13			13		
Differentia- tion degree	Low	22	9	12.472	0.000		10	10.831	0.001	11	12.414	0.000
	High school differentiation	18	17				17			18		
Clinical stages	Istage	11	5	7.653	0.022		8	4.359	0.113	9	1.593	0.451
	IIstage	19	11				10			12		
	III~IVstage	10	10				9			8		
Lymphatic metastasis	Yes	28	24	17.603	0.000		26	27.356	0.000	26	19.399	0.000
	nothing	12	2				1			3		

表 3 宫颈癌组织中 HSP70、eIF4E、DNMT1 表达和临床病理因素的相关性分析

Table 3 Correlation Analysis of HSP70, eIF4E, DNMT1 expression and clinicopathological factors in cervical cancer

Project	HSP70		eIF4E		DNMT1	
	r value	<i>P</i> value	r value	<i>P</i> value	r value	<i>P</i> value
The degree of differentiation	0.425	<0.01	0.641	<0.01	0.453	<0.01
Clinical staging	0.382	<0.01	0.394	<0.01	0.384	<0.01
Lymph node metastases	0.397	<0.01	0.430	<0.01	0.412	<0.01

3 讨论

宫颈癌是妇科常见的恶性肿瘤之一。根据世界流行病学调查,76%的宫颈癌发生在发展中国家,其中我国占 30%^[10]。宫颈癌是唯一病因明确的妇科恶性肿瘤,与高危人乳头瘤病毒持续感染有关,临床表现无特异性,不能仅凭症状和体征诊断,主要靠组织学检查^[11,12]。因此,宫颈癌的早期预防和检测在临床治疗中起着重要的作用。

HSP70 是一种应激蛋白,大量表达在多种肿瘤组织中^[13]。有研究显示,HSP70 在正常组织中表达较低,当发生应激状态时明显升高,其与道 BAG-1 结合蛋白能抑制 HSP70 参与蛋白质复性,从而调节凋亡信号分子的活性^[14-16]。本研究结果显示,在宫颈癌组织中 HSP70 阳性表达率为 65.00%,明显高于对照组,与分化程度、临床分期及淋巴转移之间均有密切关系,且 HSP70 与分化程度、临床分期及淋巴转移之间均呈正相关。说明,HSP70 在宫颈癌中表达较高,侵袭性较强,与宫颈癌发病有密切关系,可作为预测宫颈癌的重要分子标志物。分析是因为当细胞受到压力时,HSP70 迅速进入细胞核并包围着核仁。HSP70 在细胞质中含量较少。在应激消除后的恢复期,细胞核内的 HSP70 又返回到细胞质中,重新返回细胞核。

eIF4E 基因位于 4q21-25, eIF4E 恶性转化作用与它的选择性翻译密切相关,其高表达增高了一些细胞生长相关基因产物的翻译,eIF4E 的过表达显著改变了细胞表型促进细胞增殖和

诱导细胞转化和肿瘤形成^[17-20]。有研究显示,eIF4E 在乳腺癌、结肠癌、子宫癌等较多恶性肿瘤中呈高表达^[21,22]。国外研究显示,eIF4E 在头颈部肿瘤等多种恶性肿瘤中表达较高,且与术后复发时间、生存时间等相关^[23]。本研究结果显示,在宫颈癌组织中 eIF4E 阳性表达率为 67.50%,明显高于对照组,与分化程度、临床分期及淋巴转移之间均有密切关系,且 eIF4E 与分化程度、临床分期及淋巴转移之间均呈正相关。显示出 eIF4E 在乳腺癌的发生、发展、转移中起着重要作用,可成为预测宫颈癌转移的重要指标,且可能成为预测宫颈鳞癌浸润转移的一项指标。与王森^[24]等研究结果相似。分析可能是因为 eIF4E 是帽依赖性 mRNA 翻译过程中的限速因子,表达改变细胞表型,促进细胞增殖,诱导细胞转化和肿瘤发生。

DNMT1 是 DNA 甲基化反应的催化剂,新合成 DNA 的甲基化是维持细胞内 DNA 甲基化状态的关键酶,可抑制基因转录,促进肿瘤发生,其在肿瘤细胞中表达水平高于增生细胞,更高于正常细胞,其活性增高与肿瘤细胞的异常增殖分化密切相关^[25-28]。有研究显示,DNMT1 在宫颈癌、肺癌等多种恶性肿瘤中高表达^[29]。林薇等^[30]研究对宫颈癌组织中甲基化相关酶表达量的分析显示,DNMT1 表达上调的趋势最为显著。本研究结果显示,在宫颈癌组织中 DNMT1 阳性表达率为 72.50%,明显高于对照组,与分化程度、临床分期及淋巴转移之间均有密切关系,且 DNMT1 与分化程度、临床分期及淋巴转移之间均呈正相关。说明 DNMT1 表达异常与宫颈癌的发生关系较为密切,可

能是宫颈癌发生过程中的一个早期事件。分析是因为 DNMT1 基因是多态性,其蛋白中的组氨酸被精氨酸替代,且能抑制复合体,进而影响 DNMT1 的表达。

综上所述,在宫颈癌组织中 HSP70、eIF4E、DNMT1 的高表达和临床病理之间存在着密切关系,可促使疾病进展。

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