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结直肠癌组织 RSK4、p53 蛋白的表达及临床病理意义 *

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摘要 目的:探讨结直肠癌组织中 P90 核糖体 S6 激酶 4(RSK4)蛋白、p53 蛋白的表达及其临床病理意义。**方法**:选取我院病理科 2014 年 1 月～2016 年 5 月既往收集的结直肠癌手术后标本 70 例及同期结直肠癌癌旁组织 30 例，采用免疫组化染色检测两组标本中 RSK4 蛋白、p53 蛋白的表达情况,并分析其与结肠癌患者临床病理特征的相关性。**结果**:结直肠癌组织中 RSK4 蛋白、p53 蛋白的阳性表达率分别为 20.00%、55.71%,而癌旁组织中 RSK4 蛋白、p53 蛋白阳性表达率分别为 53.33%、10.00%,两组比较差异均具有统计学意义(P<0.05)。Ⅰ期+Ⅱ期、高分化和中分化结直肠癌组织 RSK4 蛋白的阳性表达率显著高于Ⅲ期、低分化结直肠癌(P<0.05);Ⅰ期+Ⅱ期、浸润深度(T1、T2)、未发生淋巴结转移的结直肠癌组织中 p53 蛋白阳性表达率显著的低于Ⅲ期、浸润深度(T3、T4)、发生淋巴结转移的结肠癌组织(P<0.05)。**结论**:结直肠癌组织中 RSK4 蛋白表达下调、p53 蛋白表达上调,二者可能与结直肠癌的发生和发展有关,并可能作为结肠癌诊断和预后评估的参考指标。

关键词:P90 核糖体 S6 激酶 4;p53 蛋白;结肠癌

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Expressions of RSK4 and p53 Protein in the Colorectal Cancer and the Clinicopathological Significances*

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ABSTRACT Objective: To investigate the protein expressions of P90 ribosomal S6 kinase 4 (RSK4) and p53 in the colon cancer and their clinicopathological significances. **Methods:** A total of 70 cases of colorectal cancer specimens and 30 cases of adjacent colorectal tissue specimens were collected in our hospital from January 2014 to May 2016, the expressions of RSK4 protein and p53 protein were detected using immunohistochemical staining, and the correlation of RSK4 and p53 protein expressions with the clinicopathological characteristics of colorectal cancer patients were analyzed. **Results:** The positive expression rates of RSK4 protein and p53 protein in the colorectal cancer were 20% and 55.71%, which were 53.33%, 10% in the adjacent tissues and significantly different from the colorectal cancer tissue (P<0.05); the positive expression rate of RSK4 protein in the colorectal cancer with phase I+II, high differentiation were significantly higher than those in stage III, poorly differentiated colorectal cancer (P<0.05); the positive expression rate of p53 in the colorectal cancer with phase I + II, the depth of invasion (T1, T2), no lymph node metastasis were significantly lower than those in stage III, the depth of invasion (T3, T4), lymph node metastasis of colon cancer (P<0.05). **Conclusion:** The expression of RSK4 protein was down regulated and the expression of p53 protein was up-regulated in the colorectal cancer tissues, which might be closely related to occurrence and development of colorectal cancer and be used as references for the diagnosis and prognostic prediction of colorectal cancer.

Key words: RSK4; p53 protein; Colon cancer

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结直肠癌的发病原因较为复杂,遗传因素、饮食习惯等均可以促进结直肠癌的发生。流行病学研究显示结直肠癌的发病率可达 233-555/10 万人左右，且越来越多的研究显示结直肠癌的发病率呈现上升的趋势，且病死率等预后指标恶化较为明显[1,2]。

P90 核糖体 S6 激酶 4(RSK4)蛋白是细胞周期调控重要因子,能够通过调控 G1/S 期、G0/S 期细胞比例,抑制癌细胞的过度增殖;p53 蛋白是重要的肿瘤基因编码蛋白，其对于癌细胞低分化的影响,增加了组织学分级的恶化,干预癌细胞错配修复机制的形成[5,6]。为了进一步揭示 RSK4、p53 蛋白表达情况与结直肠癌发病相关性,本研究探讨了 RSK4、p53 蛋白的异常表达及其与肿瘤患者临床病理特征的关系,结果报道如下。

1 资料与方法

1.1 一般资料

选取我院既往病理科收集的结直肠癌手术后标本 70 例，

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同期收集的结直肠癌癌旁组织 30 例。结直肠癌组中,男 39 例、女 31 例,年龄 37～77 岁,平均 56.0± 14.2 岁,其中结肠癌例、直肠癌例;TNM 分期:Ⅰ期例、Ⅱ期例、Ⅲ期例,病理学类型:腺癌例、黏液癌例,淋巴结转移例。癌旁组织中,男 15 例、女 15 例,年龄 40～72 岁,平均 54.8± 12.0 岁。两组患者的年龄、性别比较,差异均无统计学意义(P>0.05)。

1.2 纳入排除标准

1.2.1 纳入标准 (1)本研究使用的肿瘤组织标本、癌旁组织标本均来源于既往手术切除病理;(2)TNM 分期:Ⅰ期～Ⅲ期;(3)年龄 18～79 岁;(4)手术前患者均为接受放化疗、免疫治疗;(5)患者的各项资料完整。

1.2.2 排除标准 (1)患者伴有他部位恶性肿瘤;(2)既往结直肠癌手术后复发的患者;(3)手术前患者接受过放化疗及免疫治疗。

1.3 免疫组织化学检测方法

采用石蜡切片脱蜡至水,采用离子水进行反复洗涤,加入牛奶液体封闭抗体, 封闭时间为 5 min, 加入 RSK4 蛋白、p53 蛋白抗体(鼠来源,ABCUM 公司), 37 ℃ 孵育 2 h,采用磷酸盐缓冲液洗涤 3 次,滴加荧光染色标记的二抗抗体(购自 abcum 公司),37 ℃ 孵育 30 min,加入磷酸盐缓冲液进行洗涤,采用南京凯基生物制剂公司生产的显色剂进行显色,封片,镜下观察。

1.4 结果判定标准

免疫组换检测结果由我院病理科 2 位具有 5 年以上资历的医生分别读片,如果结果不一致则进行讨论后决定,判定标准为:RSK4 蛋白的阳性着色表达于细胞质、p53 蛋白的阳性着色表达于细胞核,呈黄色、棕黄色、褐色表达,(1)根据着色强度:0 分为无色、1 分为淡黄色、2 分为棕黄色、3 分为褐色、黑色;(2)根据阳性细胞比例: 阳性细胞数目所占比例≤ 10%为 1 分、阳性细胞所占比例 11%～50%为 2 分、阳性细胞数 51%～75%为 3 分、阳性细胞数所占比例 >75%为 4 分,两种积分相乘总分 <3 分为阴性、≧3 分为阳性。总分 < 3 分: "-" 表达;为 3～5 分,"+" 表达;为 6～9 分,"++" 表达;>9 分,"+++" 表达。

1.5 统计学分析

采用 SPSS18.0 进行统计学分析,采用均数± 标准差($\bar{x}\pm s$)进行统计描述,两组间比较采用 t 检验,计数资料组间比较采用 x^2 检验,以 P 值 <0.05 表示差异具有统计学意义。

2 结果

2.1 两组 RSK4 蛋白、p53 蛋白阳性表达率的比较

结直肠癌组织中的 RSK4 蛋白、p53 蛋白阳性表达率分别为 20.00%、55.71%,癌旁组织中 RSK4 蛋白、p53 蛋白阳性表达率分别为 53.33%、10.00%,两组比较差异具有统计学意义(P<0.05),见表 1、表 2。

表 1 两组 RSK4 蛋白阳性表达率的比较

Table 1 Comparison of the positive expression rate of RSK4 protein between two groups

Group	n	-	+	++	+++	positive rate(%)
Cancer tissue	70	56	14	0	0	14(20.00)
Adjacent tissue	30	14	10	4	2	16(53.33)
P						0.001

表 2 两组 p53 蛋白阳性表达率的比较

Table 2 Comparison of the positive expression rate of p53 protein between two groups

Group	n	-	+	++	+++	positive rate(%)
Cancer tissue	70	31	15	18	6	39(55.71)
Adjacent tissue	30	27	3	0	0	3(10.00)
P						<0.001

2.2 结直肠癌组织中 RSK4 蛋白、p53 蛋白阳性表达率与患者临床病理特征的关系

Ⅰ期 +Ⅱ期、高分化和中分化结直肠癌组织中的 RSK4 蛋白阳性率显著的高于Ⅲ期、低分化结直肠癌,差异具有统计学意义(P<0.05);Ⅰ期 +Ⅱ期、浸润深度(T1、T2)、未发生淋巴结转移的结直肠癌组织中 p53 蛋白阳性表达率显著的低于Ⅲ期、浸润深度(T3、T4)、发生淋巴结转移的结肠癌组织,两组比较差异具有统计学意义(P<0.05),表 3、表 4。

3 讨论

结直肠癌的现阶段临床上总体治疗有效率不足 25%,包括手术或者联合放化疗等综合性治疗措施的临床病情缓解率较低 [7,8]。同时对于结直肠癌的早期发病过程缺乏有效的筛查指标,虽然 CEA 或者 CA125 等上皮肿瘤糖蛋白成分能够在一定程度上提高结直肠癌癌的诊断效率,但其筛查的灵敏度或者特异度等的局限性仍然较为明显[9,10]。

结直肠癌的发病机制较为复杂,遗传因素、基因突变等均可能增加癌细胞早期病变的风险。基因水平的异常近年来被认为是影响到恶性肿瘤发生的核心因素,基因突变或者基因表达调控的异常增加了癌细胞过度扩增的风险,导致癌细胞的正常分化或者促凋亡过程明显失常[11]。RSK4 是核糖体修饰因子,其对于核糖体羧基末端的修饰作用能够降低染色体 DNA 的错配风险, 并为基因错配修复因子 cyc 活性的维持提供保障[12,13]。RSK4 具有对于癌细胞低分化的抑制作用降低了癌细胞对于血管内皮或者淋巴管内皮的粘附能力,对于恶性肿瘤的进展具有一定的抑制作用;p53 蛋白对于 notch 信号通路或者 akt 信号通

表 3 结直肠癌组织中 RSK4 蛋白表达率与患者临床病理特征的关系

Table 3 The relationship between the expression of RSK4 protein and clinicopathological characteristics of colorectal cancer

Clinicopathologic characteristics	RSK4- positive(n=14)		RSK4- negative(n=56)		P
	n	%	n	%	
Age(year)					0.546
≥ 60	5	35.71%	25	44.64%	
<60	9	64.29%	31	55.36%	
Gender					0.47
male	9	64.29%	30	53.57%	
female	5	35.71%	26	46.43%	
Depth of invasion					0.094
T+T2	10	71.43%	26	46.43%	
T3+T4	4	28.57%	30	53.57%	
TNM staging					0.021
Ⅰ+Ⅱ	12	85.71%	29	51.79%	
Ⅲ	2	14.29%	27	48.21%	
Degree of divergence					0.041
high+ middle	11	78.57%	27	48.21%	
poorly	3	21.43%	29	51.79%	
Lymph node metastasis					0.052
yes	5	35.71%	36	64.29%	
no	9	64.29%	20	35.71%	
CEA- positive					0.401
positive	5	35.71%	27	48.21%	
negative	9	64.29%	29	51.79%	
CA199- positive					0.729
positive	6	42.86%	29	51.79%	
negative	8	57.14%	27	48.21%	

表 4 结直肠癌组织中 p53 蛋白阳性表达率与患者临床病理特征的关系

Table 4 The relationship between the expression of p53 protein and clinicopathological characteristics of colorectal cancer

Clinicopathologic characteristics	p53- positive(n=39)		p53- negative(n=31)		P
	n	%	n	%	
Age(year)					0.532
≥ 60	18	46.15%	12	38.71%	
<60	21	53.85%	19	61.29%	
Gender					0.402
male	20	51.28%	19	61.29%	
female	19	48.72%	12	38.71%	
Depth of invasion					0.004
T+T2	14	35.90%	22	70.97%	
T3+T4	25	64.10%	9	29.03%	
TNM staging					0.001

表 4 结直肠癌组织中 p53 蛋白阳性表达率与患者临床病理特征的关系(续表)

Table 4 The relationship between the expression of p53 protein and clinicopathological characteristics of colorectal cancer

Clinicopathologic characteristics	p53- positive(n=39)		p53- negative(n=31)		P
	n	%	n	%	
Ⅰ+Ⅱ	16	41.03%	25	80.65%	
Ⅲ	23	58.97%	6	19.35%	
Degree of divergence					0.126
high+ middle	18	46.15%	20	64.52%	
poorly	21	53.85%	11	35.48%	
Lymph node metastasis					<0.001
yes	30	76.92%	11	35.48%	
no	9	23.08%	20	64.52%	
CEA- positive					0.572
positive	19	48.72%	13	41.94%	
negative	20	51.28%	18	58.06%	
CA199- positive					0.47
positive	21	53.85%	14	45.16%	
negative	18	46.15%	17	54.84%	

路的激活作用促进肠道上皮细胞核分裂象的异常,导致癌细胞对于肠道基底膜层的突破作用明显增加[14-16]。

在本研究中,结直肠癌病灶组织中 RSK4 蛋白的表达明显下降,而 P53 蛋白的表达明显上升,提示两种蛋白均可能参与到了结直肠癌的发生发展过程。P53 的高表达可以通过影响到下列几个方面的因素促进结直肠癌的病情进展[17-20]:(1)促进癌细胞早期细胞核分裂速度的增加,并导致癌细胞错配基因切除机制的丧失;(2) 影响结直肠上皮腺体细胞的异型性的变化,癌细胞异型性的改变导致结直肠癌患者组织学分级的恶化。而 RSK4 蛋白表达的下降失去了其对于恶性肿瘤发生的保护性作用,这主要体现在 RSK4 蛋白对于结直肠癌患者癌细胞周期调控及细胞凋亡诱导因子 a 的沉默作用有关。赵喜连等[21,22]随访分析了 83 例样本量的结直肠癌病灶组织, 发现 p53 蛋白在低分化或者临床分期较晚的患者中表达浓度较高,其表达浓度的上升与肿瘤患者的临床预后具有密切的关系。结直肠癌 I 期、II 期或者癌细胞分化程度较好的患者 RSK4 蛋白表达阳性率往往较高,而发生了淋巴结转移或者组织浸润深度较深的结直肠癌患者 P53 蛋白的表达阳性率往往较高,两种不同生物蛋白对于结直肠癌临床病理特征的影响可以从下列方面进行理解[23-25]:(1)P53 蛋白能够促进癌细胞对于结直肠上皮间质成分的浸润,促进癌细胞通过网膜、淋巴进行转移,导致浸润深度的加深;(2)RSK4 蛋白表达阳性率的下降, 失去了其对于癌细胞分化调控的保护性作用,癌细胞的低分化特征更为明显。

综上所述,结直肠癌组织中 RSK4 蛋白表达下调、p53 蛋白表达上调,并且与患者临床分期、癌细胞分化程度及浸润深度等指标密切相关, 二者可能与结直肠癌的发生和发展有关,并可能作为结肠癌诊断和预后评估的参考指标。

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