doi: 10.13241/j.cnki.pmb.2018.19.028

Beclin1 与 p53 在唾液腺多形性腺瘤和癌在唾液腺多形性腺瘤中的表达及与临床病理因素的关系研究 *

曹星华 胡温庭△ 孙学辉 范 欣 董 超 栾可峰

（潍坊医学院附属医院口腔科 山东 潍坊 261041）

摘要 目的:探讨自噬体相关基因 Beclin1 与 p53 基因在唾液腺多形性腺瘤(PA)和癌在唾液腺多形性腺瘤(CPA)中的表达及其与临床病理因素的关系。**方法:**选择 2013 年 1 月至 2017 年 8 月于我院手术切除的 PA 标本 45 例作为 PA 组,CPA 标本 32 例作为 CPA 组，正常腮腺组织 30 例作为对照组，应用免疫组化 SP 法对三组 Belin1 与 p53 基因表达情况进行检测，分析 CPA 组 Beclin1、p53 表达情况与临床病理因素关系及 Beclin1、p53 表达的相关性。**结果:**三组 Beclin1、p53 阳性表达率存在统计学差异,CPA 组 Beclin1 阳性表达率低于 PA 组和对照组,CPA 组和 PA 组 p53 阳性表达率高于对照组,且 CPA 组高于 PA 组(P<0.05)。CPA 组 Beclin1、p53 表达情况与 TNM 分期、淋巴结转移有关,TNM 分期为 III-IV 期患者 Beclin1 阳性表达率低于 I-II 期患者,p53 阳性表达率高于 I-II 期患者,淋巴结转移患者 Beclin1 阳性表达率低于无淋巴结转移患者,p53 阳性表达率高于无淋巴结转移患者,差异均有统计学意义(P<0.05),CPA 组 Beclin1、p53 表达情况与年龄、性别、肿瘤直径、侵袭性无关(P>0.05)。经 Spearman 相关性分析可得,CPA 患者 Beclin1 和 p53 的表达呈负相关关系(r=-0.839,P=0.000)。**结论:**PA 及 CPA 中存在 Beclin1 异常低表达,p53 异常高表达,CPA 患者 Beclin1、p53 表达情况与 TNM 分期、淋巴结转移有关,且两者表达呈负相关。

关键词:唾液腺多形性腺瘤;癌在唾液腺多形性腺瘤;Beclin1;p53;相关性

中图分类号:R739.8 **文献标识码:**A **文章编号:**1673-6273(2018)19-3725-04

Expressions of Beclin1 and p53 in Pleomorphic Adenoma, Carcinoma in Pleomorphic Adenoma and its Relationship with Clinicopathological Factors*

CAO Xing-hua, HU Wen-ting△, SUN Xue-hui, FAN Xin, DONG Chao, LUAN Ke-feng

(Department of Stomatology, Affiliated Hospital of Weifang Medical University, Weifang, Shandong, 261041, China)

ABSTRACT Objective: To analyze the expressions of autophagic related genes Belin1 and p53 in pleomorphic adenoma(PA), carcinoma in pleomorphic adenoma (CPA) and its relationship with clinicopathological factors. **Methods:** 45 cases of PA excised in our hospital from January 2013 to August 2017 were selected as PA group, 32 cases of CPA specimens as CPA group, 30 normal parotid tissue as control group, the expression of Belin1 and p53 gene in three groups were detected by immunohistochemical SP method, the relationship between the expression of Beclin1 and p53 in the CPA group and the clinicopathological factors, the correlation of the expression of Beclin1 and p53 were analyzed. **Results:** There were statistical differences in the positive rates of Beclin1 and p53 in the three groups, the positive expression rate of Beclin1 in CPA group were lower than those in PA group and control group, the positive expression rate of p53 in CPA group were lower than those in PA group and control group, and the CPA group was higher than the PA group (P<0.05). The ex- pression of Beclin1 and p53 in group CPA were related to TNM staging and lymph node metastasis, the positive rate of Beclin1 in TNM stage for III-IV patients was lower than that in I-II stage, the positive expression rate of p53 was higher than that in I-II stage, the positive rate of Beclin1 in patients with lymph node metastasis was lower than that of patients without lymph node metastasis, the positive expression rate of p53 was higher than that of the patients without lymph node metastasis, the differences were statistically significant (P<0.05). The expression of Beclin1 and p53 in group CPA were not related to age, sex, tumor diameter and invasiveness (P>0.05). Spearman correlation analysis showed that the expression of Beclin1 and p53 in CPA patients were negatively correlated (r=-0.839, P=0.000). **Conclusion:** The expression of Beclin1 is low abnormal and p53 is high abnormal in PA and CPA,the expression of Beclin1 and p53 in patients with CPA are related to TNM staging and lymph node metastasis, and the expression of the two is negatively correlated.

Key words: Pleomorphic adenoma; Carcinoma in pleomorphic adenoma; Beclin1; p53; Correlation

Chinese Library Classification(CLC):R739.8 Document code: A

Article ID: 1673-6273(2018)19-3725-04

* 基金项目:山东省自然科学基金项目(ZR2010HL014)

作者简介:曹星华(1982-),男,硕士,主治医师,从事口腔颌面部肿瘤方面的研究,E-mail:mqgowe@163.com

△ 通讯作者:胡温庭(1963-),男,本科,主任医师,从事口腔颌面部肿瘤方面的研究,E-mail:cqgnde@163.com

(收稿日期:2018-03-07 接受日期:2018-03-31)

前言

唾液腺多形性腺瘤(pleomorphic adenoma,PA)是腮腺区常见的肿瘤,发病率约占腮腺区肿瘤的 50%以上,占唾液腺瘤的 51.4%-67.2%[1,2]。PA 膨胀性生长不仅会影响患者的容貌,同时具有潜在的恶性生物学行为,手术切除后易复发[3,4]。有报道显示,90%的癌在多形性腺瘤(carcinoma in pleomorphic adenoma,CPA)是由 PA 恶变所致,如不给予及时有效的治疗,可危及患者的生命安全[5]。目前关于 PA 和 CPA 的发病机制仍未完全明确,所以关于这两种疾病的鉴别诊断和治疗具有一定的困难。自噬体相关基因 Beclin1 是一段相对保守的基因序列,酵母与哺乳动物具有同源的基因序列,是自噬的主要执行者[6,7]。近年来研究发现在乳腺癌、甲状腺癌、卵巢癌中均存在 Beclin1 的低表达,其表达缺失可能是恶性肿瘤发生的重要机制之一[8,9]。p53 是目前已知的最重要的肿瘤抑制基因,在细胞凋亡、细胞周期调控中起到重要作用,与恶性肿瘤的发生、发展有密切关系[10,11]。本研究分析了 Beclin1 与 p53 在 PA 和 CPA 中的表达情况及其与临床病理因素的关系,旨在为 PA 和 CPA 的诊断治疗提供依据,现作如下报道。

1 资料和方法

1.1 一般资料

选择 2013 年 1 月至 2017 年 8 月于我院行手术切除的 PA 标本 45 例为 PA 组,CPA 标本 32 例为 CPA 组,纳入标准:(1)所有标本均为手术切除后留取;(2) 术后经高年资病理医生诊断确诊;(3)患者病历资料齐全,对研究知情同意并签署知情同意书,排除标准:(1)多次接受手术治疗者;(2)术前经放疗、化疗和免疫治疗者;(3)预计生存期 <12 个月。CPA 组男 11 例,女 21 例,年龄 38-72 岁,平均(62.27± 6.73)岁;肿瘤直径:≤ 4 cm 24 例,>4 cm 8 例;TNM 分期:I 期 4 例,II 期 11 例,III 期 12 例,IV 期 5 例;存在侵袭性 18 例,无侵袭性 14 例;有淋巴结转移 12 例,无淋巴结转移 20 例。PA 组男 14 例,女 31 例,年龄 35-73 岁,平均(61.56± 7.22)岁;肿瘤直径:≤ 4 cm 30 例,>4 cm 15 例。选择同期因外伤手术切除的腮腺正常组织 30 例作为对照组,其中男 11 例,女 19 例,年龄 35-70 岁,平均(61.05± 7.02)岁。各组研究对象年龄、性别比较差异无统计学意义(P>0.05),所有标本均经甲醛固定,石蜡包埋,制成 4 μm 连续切片,本研究经医院伦理委员会研究同意。

1.2 试剂来源

兔抗人 Beclin1 单克隆抗体(购自美国 Adcam 公司),兔抗人 p53 单克隆抗体 (购自美国 Santa Cruz 公司),DAB 显色剂以及免疫组化试剂盒购自武汉博士德生物工程有限公司。

1.3 研究方法

应用免疫组化 SP 法对三组 Belin1 与 p53 基因表达情况进行检测,具体步骤如下:将所有石蜡包埋的切片进行脱蜡,并放入梯度乙醇溶液水化,高温抗原修复,随后将切片置入 3% H_2O_2 中室温条件下孵育 5-10 min,消除内源性过氧化酶活性。蒸馏水冲洗后浸泡到 PBS 缓冲液中 5 min,应用山羊血清进行封闭,滴加 1:100 比例稀释的 Beclin1、p53 单克隆Ⅰ抗,在 4℃条件下过夜,次日应用 PBS 缓冲液冲洗,滴加生物学 II 抗,避光孵育 30 min 后应用 PBS 冲洗,然后加入链霉亲和素 - 生物素 - 过氧化物酶,孵育 15 min,然后进行 DAB 显色,梯度乙醇脱水,苏木精复染,中性树胶封片,置于显微镜下观察。应用 PBS 缓冲液代替一抗作为阴性对照,用试剂公司提供的样本作为阳性对照。

1.4 评价标准[12]

采用 400 倍光镜观察切片,每张切片随机选取 10 个视野进行观察和计数,每个视野观察 100 个细胞,Beclin1 主要表达于细胞质和细胞膜上,出现棕黄色颗粒为阳性表达,P53 主要表达于细胞核内,出现棕黄色颗粒为阳性表达。根据阳性细胞百分比和染色强度进行评分。(1)阳性细胞所占百分比:0 分,无阳性细胞;1 分,阳性细胞 <30%;2 分,阳性细胞 30-70%;3 分,阳性细胞 >70%。(2)染色强度:0 分,无染色;1 分,染色呈浅黄色;2 分,染色呈黄色;3 分,染色为棕黄色。将以上评分进行累加 0-3 分为阴性(-),4 分及以上为阳性(+)。

1.5 统计学方法

应用 SPSS25.0 统计软件进行数据分析,计数资料以%表示,实施 x^2 检验,计量资料以($\bar{x}$± s)表示,实施 t 检验,相关性分析使用 Spearman 相关性分析,P<0.05 为差异有统计学意义。

2 结果

2.1 三组 Beclin1、p53 表达情况比较

三组 Beclin1、p53 阳性表达率存在统计学差异,CPA 组 Beclin1 阳性表达率低于 PA 组和对照组,CPA 组和 PA 组 p53 阳性表达率高于对照组,且 CPA 组高于 PA 组,差异均有统计学意义(P<0.05)。见表 1。

表 1 三组 Beclin1、p53 表达情况比较[n(%)]

Table 1 Comparison of expression of Beclin1 and p53 in the three groups [n(%)]

Groups	n	Beclin1		p53	
		-	+	-	+
CPA group	32	15(46.88)	17(53.13)[ab]	8(25.00)	24(75.00)[ab]
PA group	45	11(24.44)	34(75.56)	36(80.00)	9(20.00)[a]
Control group	30	3(10.00)	27(90.00)	29(96.67)	1(3.33)
x^2		10.934		41.652	
P		0.004		0.000	

Note: compared with the control group, [a]P<0.05; compared with the PA group, [b]P<0.05.

2.2 CPA 组 Beclin1、p53 表达情况与临床病理因素关系分析

CPA 组 Beclin1、p53 表达情况与 TNM 分期、淋巴结转移有关，TNM 分期为 III-IV 期患者 Beclin1 阳性表达率低于 I-II 期患者，p53 阳性表达率高于 I-II 期患者，淋巴结转移患者 Beclin1 阳性表达率低于无淋巴结转移患者，p53 阳性表达率高于无淋巴结转移患者，差异均有统计学意义（P<0.05），CPA 组 Beclin1、p53 表达情况与年龄、性别、肿瘤直径、侵袭性无关（P>0.05）。见表 2。

表 2 CPA 组 Beclin1、p53 表达情况与临床病理因素关系分析[n(%)]

Table 2 Analysis of the relationship between the expression of Beclin1, p53 and the clinicopathological factors in group CPA[n(%)]

Factors		n	Beclin1		x^2	P	p53		x^2	P
			-	+			-	+		
Age(year)	<60	20	9(45.00)	11(55.00)	0.075	0.784	5(25.00)	15(75.00)	0.000	1.000
	≥ 60	12	6(50.00)	6(50.00)			3(25.00)	9(75.00)		
Gender	Male	11	5(45.45)	6(54.55)	0.014	0.907	3(27.27)	8(72.73)	0.046	0.830
	Female	21	10(47.62)	11(52.38)			5(23.81)	16(76.19)		
Tumor diameter(cm)	≤ 4	24	11(45.83)	13(54.17)	0.042	0.838	4(16.67)	20(83.33)	0.274	0.601
	>4	8	4(50.00)	4(50.00)			2(25.00)	6(75.00)		
TNM staging	I-IIstaging	15	2(13.33)	13(86.67)	12.756	0.000	7(46.67)	8(53.33)	7.069	0.008
	III-IVstaging	17	13(76.47)	4(23.53)			1(5.88)	16(94.12)		
Invasiveness	No	14	6(42.86)	8(57.14)	0.161	0.688	4(28.57)	10(71.43)	0.169	0.681
	Yes	18	9(50.00)	9(50.00)			4(22.22)	14(77.78)		
Lymph node metastasis	No	12	9(75.00)	3(25.00)	6.099	0.014	0(0.00)	12(100.00)	6.400	0.011
	Yes	20	6(30.00)	14(70.00)			8(40.00)	12(60.00)		

2.3 CPA 患者 Beclin1、p53 表达的相关性分析

经 Spearman 相关性分析可得，CPA 患者 Beclin1 和 p53 的表达呈负相关关系（r=-0.839，P=0.000）。见表 3。

表 3 CPA 患者 Beclin1、p53 表达的相关性分析

Table 3 The correlation analysis of expression of Beclin1, p53 in CPA patients

		Beclin1		r	P
		+	-		
p53	+	15	9	-0.839	0.000
	-	2	6		

3 讨论

自噬是真核生物细胞的一项正常生理功能，它以细胞质中出现自噬体为主要体征，并以细胞 " 自我吞噬消化 " 为中心而发生的一种机制[13,14]。正常情况下机体细胞处于代谢的动态平衡中，细胞可以通过自噬起到维持细胞物质代谢、调节细胞生长分化、重建细胞结构等作用。近年来随着研究的不断深入，有学者发现，自噬在肿瘤的发生、发展中起到重要的作用[15]。Beclin1 是近年来新发现的自噬相关基因，是酵母 Atg6 同源蛋白 B 细胞淋巴瘤蛋白质 2 的相互作用蛋白质基因[16,17]。研究发现，Beclin1 编码的蛋白质可以促进真核细胞形成自噬体，是自噬活动的主要执行者[18]。张健等通过对乳腺癌、乳腺增生和正常乳腺组织的观察发现，乳腺癌组织中存在 Beclin1 的异常低表达，并认为 Beclin1 表达缺失与乳腺癌的发生发展有关[19,20]。陈飞等通过对宫颈癌患者的观察发现，宫颈癌组织中存在 Beclin1 的异常低表达，其表达水平与肿瘤恶性程度呈负相关[21,22]。但目前关于 CPA 和 PA 中 Beclin1 表达情况仍不明确。关于 Beclin1 与其他癌基因、抑癌基因的相互作用仍不了解。p53 是目前研究最多的一种抑癌基因，位于人类 17 号染色体短臂上，相关研究表明，p53 基因在多种良性、恶性肿瘤发生、发展中起到重要作用[23,24]。p53 基因分为野生型和突变型两个亚型，当野生型 p53 基因丢失时，突变型 p53 将失去抑制肿瘤的功能，并导致细胞发生癌变[25,26]。

本研究通过对 PA 标本、CPA 标本及腮腺正常组织对照发现，三组 Beclin1、p53 阳性表达率存在统计学差异，CPA 组 Beclin1 阳性表达率低于 PA 组和对照组，CPA 组和 PA 组 p53 阳性表达率高于对照组，且 CPA 组高于 PA 组（P<0.05）。表明 PA 及 CPA 中存在 Beclin1 异常低表达，p53 异常高表达。PA 是一种具有潜在恶性生物学行为的肿瘤，多次复发可能增加癌变发生的概率，推测 PA 患者的 Beclin1 低表达、p53 的高表达可能促进 PA 癌变的发生，而 CPA 标本中 Beclin1 阳性表达率更低，p53 阳性表达率更高，提示在 PA 向 CPA 发展中 Beclin1 和

p53 起到了重要作用。临床上可以通过对患者 Beclin1、p53 表达情况的检测为 PA 和 CPA 鉴别诊断提供依据,同时也可以为 PA 的预后判断提供参考。本研究结果还显示 CPA 患者 Beclin1、p53 表达情况与 TNM 分期、淋巴结转移有关(P<0.05),与年龄、性别、肿瘤直径、侵袭性无关(P>0.05)。表明 Beclin1、p53 与 CPA 的恶性程度和淋巴结转移有关,Beclin1、p53 在 CPA 发生、发展中起到了重要作用。可能是由于 Beclin1 的表达缺失使细胞自噬功能下降,并进一步影响细胞的生长、分化和增殖,导致细胞癌变和转移[27,28]。而 p53 表达增高则是细胞自我调节的结果,当细胞所处的环境、应激和定位不同时,p53 表达情况不同,当突变型 p53 表达增高时,可导致细胞发生癌变。目前关于自噬现象与其他癌基因、抑癌基因的关系仍不十分明确,大多数学者认为 p53 可能通过多个信号通路调控自噬的发生[29,30]。本研究结果经 Spearman 相关性分析显示,CPA 患者 Beclin1 和 p53 的表达呈负相关关系(P<0.05),提示 p53 可能与 Beclin1 相互作用,调控细胞自噬,并在 CPA 发生、发展中起到重要作用。其具体机制有待于进一步研究证实。

综上所述,在 PA 及 CPA 中,Beclin1 存在低表达、p53 存在高表达,并且 Beclin1、p53 表达情况与 CPA 患者 TNM 分期、淋巴结转移有关,且呈负相关关系,临床上可为 PA 和 CPA 鉴别诊断提供参考依据。

参 考 文 献(References)

[1] Korba M, Chloupek A, Dąbrowski J, et al. Pleomorphic adenoma - the results of a retrospective analysis of 104 patients treated at the Clinical Department of Cranio-Maxillofacial Surgery, Clinic of Otolaryngology and LaryngologicOncology of the Military Institute of Medicine[J]. Otolaryngol Pol, 2017, 71(4): 34-36

[2] Passi D, Ram H, Dutta SR, et al. Pleomorphic Adenoma of Soft Palate: Unusual Occurrence of the Major Tumor in Minor Salivary Gland-A Case Report and Literature Review [J]. J Maxillofac Oral Surg, 2017, 16(4): 500-505

[3] Franco-Garrocho LE, Pérez-Frutos JR, Sánchez-Acuña JG, et al. Use of transmandibular approach for resection of a relapse pleomorphic adenoma on the parapharyngeal space [J]. Rev Med Inst Mex Seguro Soc, 2017, 55(6): 801-803

[4] Accorona R, Barbieri D, Farina D, et al. Intracapsular carcinoma ex-pleomorphic adenoma of the parapharyngeal space: report of two cases and review of the literature [J]. Tumori, 2017, 103 (Suppl. 1): e73-e77

[5] 夏亮,田臻.唾液腺多形性腺癌恶变分子机制研究进展[J].医学综述, 2016, 22(3): 500-504
Xia Liang, Tian Zhen. Molecular Mechanisms of Malignant Transformation in Salivary Gland Pleomorphic Adenoma[J]. Medical Recapitulate, 2016, 22(3): 500-504

[6] Majdoul S, Cosette J, Seye AK, et al. Peptides derived from evolutionarily conserved domains in Beclin-1 and Beclin-2 enhance the entry of lentiviral vectors into human cells[J]. J Biol Chem, 2017, 292(45): 18672-18681

[7] Silva CA, Martinez EF, Demasi AP, et al. Cellular senescence and autophagy of myoepithelial cells are involved in the progression of in situ areas of carcinoma ex-pleomorphic adenoma to invasive carcinoma. An in vitro model[J]. J Cell Commun Signal, 2015, 9(3): 255-265

[8] Pradhan AK, Talukdar S, Bhoopathi P, et al. mda-7/IL-24 Mediates Cancer Cell-Specific Death via Regulation of miR-221 and the Beclin-1Axis[J]. Cancer Res, 2017, 77(4): 949-959

[9] Zhang F, Wang B, Long H, et al. Decreased miR-124-3p Expression Prompted Breast Cancer Cell Progression Mainly by Targeting Beclin-1[J]. Clin Lab, 2016, 62(6): 1139-1145

[10] 徐燕,蔡媛,马宁,等.肺癌组织中 PCNA、p63 和 p53 蛋白的表达及临床意义[J].现代生物医学进展, 2017, 17(10): 1924-1926, 1930
Xu Yan, Cai Yuan, Ma Ning, et al. Expression and Clinical Implication of PCNA, p63 and p53 in Lung Cancers [J]. Progress in Modern Biomedicine, 2017, 17(10): 1924-1926, 1930

[11] Koyama R, Tamura M, Nakagaki T, et al. Identification and characterization of a metastatic suppressor BRMS1L as a target gene of p53 [J]. Cancer Sci, 2017, 108(12): 2413-2421

[12] 陈国昆,吴益华,张世周,等.p53 和自噬相关基因 Beclin1 在唾液腺多形性腺瘤和癌在多形性腺瘤中的表达及意义[J].上海口腔医学, 2014, 23(2): 214-218
Chen Guo-kun, Wu Yi-hua, Zhang Shi-zhou, et al. Expression and clinical significance of p53 and autophagy-related gene Beclin1 in salivary pleomorphic adenoma and carcinoma in pleomorphic adenoma [J]. Shanghai Journal of Stomatology, 2014, 23(2): 214-218

[13] Zheng L, Li H, Mo Y, et al. Autophagy inhibition sensitizes LY3023414-induced anti-glioma cell activity in vitro and in vivo[J]. Oncotarget, 2017, 8(58): 98964-98973

[14] Yang W, Li L, Huang X, et al. Levels of Leydig cell autophagy regulate the fertility of male naked mole-rats [J]. Oncotarget, 2017, 8(58): 98677-98690

[15] Inoue H, Hanawa N, Katsumata SI, et al. Iron deficiency induces autophagy and activates Nrf2 signal through modulating p62/SQSTM [J]. Biomed Res, 2017, 38(6): 343-350

[16] Du H, Che J, Shi M, et al. Beclin 1 expression is associated with the occurrence and development of esophageal squamous cell carcinoma [J]. Oncol Lett, 2017, 14(6): 6823-6828

[17] Li X, Wu XQ, Deng R, et al. CaMKII-mediated Beclin 1 phosphorylation regulates autophagy that promotes degradation of Id and neuroblastoma cell differentiation[J]. Nat Commun, 2017, 8(1): 1159

[18] 邬琳, 郭金珠.EGFR 和自噬标记蛋白 Beclin1 在宫颈癌组织中的表达及意义[J].实用癌症杂志, 2017, 32(7): 1079-1081
Wu Lin, Guo Jin-zhu. Expression and Significance of EGFR and Autophagy Marker Protein Beclin1 in Human Cervical Cancer [J]. The Practical Journal of Cancer, 2017, 32(7): 1079-1081

[19] 张健, 吴爱国, 王梦川, 等. 相关成纤维细胞自噬调控对乳腺癌 MCF-7 细胞上皮间质转化影响[J].中华肿瘤防治杂志, 2017, 24(9): 589-595
Zhang Jian, Wu Ai-guo, Wang Meng-chuan, et al. Influences of autophagic regulations of carcinoma associated fibroblasts on the EMT process of breast cancer MCF-7 cell line[J]. Chinese Journal of Cancer Prevention and Treatment, 2017, 24(9): 589-595

[20] Jakhar R, Paul S, Bhardwaj M, et al. Astemizole-Histamine induces Beclin-1-independent autophagy by targeting p53-dependent crosstalk between autophagy and apoptosis [J]. Cancer Lett, 2016, 372 (1): 89-100

(下转第 3776 页)

[12] Tang C, Hua W L. Naloxone combined with Xingnaojing Injection in the treatment of acute severe alcoholism: clinical effect [J]. Guizhou Medical Journal, 2016, 40(10): 1043-1045

[13] Pace M C, Passavanti M B, Aurilio C, et al. Polydatin Administration Improves Serum Biochemical Parameters and Oxidative Stress Markers During Chronic Alcoholism: A Pilot Study [J]. In Vivo, 2015, 29 (3): 405-406

[14] Xu T. To observe the curative effect of nalmefene poisoning combined with Xingnaojing Injection in the treatment of acute alcoholism [J]. Chin J Integr Med Cardio, 2014, 12(2): 200-201

[15] Chen Z G, Xie M M. Xingnaojing applied in patients with severe alcohol poisoning emergency[J]. Liaoning J Tradit Chin Med, 2014, 41 (4): 720-722

[16] Liu C. Chinese medicine Xingnaojing and hemodialysis in acute severe alcoholism in patients with combined application of research[J]. Guid J Tradit Chin Med Pharm, 2014, 20(13): 85-87

[17] Wang Y X, Zhang Y Q, Su G L, et al. Effect of Xingnaojing Injection on acute oxidative stress in patients with severe alcohol poisoning[J]. J Shanxi Med, 2017, 5(3): 305-307

[18] Chen B, Zheng A, Chen Y Q. Analysis of curative effect of Xingnaojing poisoning hyperoxia solution in the treatment of acute alcoholism [J]. J Emerg Tradit Chin Med, 2014, 23(4): 765-766

[19] Li Y L. The clinical curative effect observation of Xingnaojing Injection in the treatment of acute alcoholism [J]. Pract J Cardiac Cereb Pneum Vasc Dis, 2014, 22(1): 110-111

[20] Ma C L, Chen H B. Naloxone combined with Xingnaojing Injection in the treatment of acute severe alcoholism efficacy[J]. Shanxi Med J, 2016, 45(24): 2891-2892

[21] Wei W. Effects of different treatment regimens on cognitive function in patients with chronic alcoholic encephalopathy [J]. Pract J Cardiac Cereb Pneum Vasc Dis, 2014, 4(9): 68-69

[22] Luo Q, Tu X, Xiong F, et al. The effect of Xingnaojing injection combined with naloxone in treatment of acute alcoholism in economic analysis[J]. Northwest Pharm J, 2015, 30(6): 747-750

[23] Su Q Y. Effects of Puerarin Injection combined with western medicine on neurotransmitter and oxidative stress in patients with alcoholism[J]. World J Integr Tradit West Med, 2016, 11(6): 844-847

[24] Stepien M, Fedirko V, Duarte-Salles T, et al. Prospective association of liver function biomarkers with development of hepatobiliary cancers[J]. Cancer Epidemiol, 2016, 40(1): 179-180

[25] Qin X, Chen Y H. Effect of Xingnaojing injection combined with adjuvant treatment effect of acute alcoholism on serum beta peptide in coffee, SOD and MDA levels [J]. J Clin Med Prac, 2016, 20(17): 142-144

(上接第 3728 页)

[21] 陈飞,余婷婷,李俊,等.宫颈癌中自噬标记蛋白 Beclin1、p62 的表达及其临床意义[J].实用癌症杂志, 2017, 32(2): 218-220
Chen Fei, Yu Ting-ting, Li Jun, et al. Expression of Cervical Autophagy Marker Protein Beclin1, p62 and Clinical Significance [J]. The Practical Journal of Cancer, 2017, 32(2): 218-220

[22] Jung YY, Lee YK, Koo JS. The potential of Beclin 1 as a therapeutic target for the treatment of breast cancer[J]. Expert Opin Ther Targets, 2016, 20(2): 167-178

[23] Hanks TS, Gauss KA. Pleomorphic adenoma gene-like 2 regulates expression of the p53 family member, p73, and induces cell cycle block and apoptosis in human promonocytic U937 cells[J]. Apoptosis, 2012, 17(3): 236-247

[24] Faur AC, Sas I, Motoc AG, et al. Ki-67 and p53 immunostaining assessment of proliferative activity in salivary tumors [J]. Rom J Morphol Embryol, 2015, 56(4): 1429-1439

[25] Alaizari NA, Tarakji B, Al-Maweri SA, et al. p53 expression in pleomorphic adenoma of salivary glands: A systematic review and meta-analysis[J]. Arch Oral Biol, 2015, 60(9): 1437-1441

[26] Ferreira JC, Morais MO, Elias MR, et al. Pleomorphic adenoma of oral minor salivary glands: An investigation of its neoplastic potential based on apoptosis, mucosecretory activity and cellular proliferation [J]. Arch Oral Biol, 2014, 59(6): 578-585

[27] Li X, Wu XQ, Deng R, et al. CaMKII-mediated Beclin 1 phosphorylation regulates autophagy that promotes degradation of Id and neuroblastoma cell differentiation[J]. Nat Commun, 2017, 8(1): 1159

[28] Liu L, Zhao WM, Yang XH, et al. Effect of inhibiting Beclin-1 expression on autophagy, proliferation and apoptosis in colorectal cancer[J]. Oncol Lett, 2017, 14(4): 4319-4324

[29] Alaizari NA, Tarakji B, Al-Maweri SA, et al. p53 expression in pleomorphic adenoma of salivary glands: A systematic review and meta-analysis[J]. Arch Oral Biol, 2015, 60(9): 1437-1441

[30] Cowen LE, Tang Y. Identification of nonsense-mediated mRNA decay pathway as a critical regulator of p53 isoform β[J]. Sci Rep, 2017, 7(1): 17535