

doi: 10.13241/j.cnki.pmb.2020.09.040

胃癌患者中 CEA、AEP 的表达及相关性分析 *

芦淑娟¹ 张晓艳¹ 关佳楠² 孙 琥³ 张君杰³

(沈阳市第五人民医院 1 病理科; 2 肿瘤外科 辽宁 沈阳 110023; 3 沈阳医学院附属中心医院病理科 辽宁 沈阳 110024)

摘要 目的:探讨胃癌患者中癌胚抗原(CEA)、天冬酰胺内肽酶(AEP)的表达及相关性分析。**方法:**回顾性分析 2016 年 9 月至 2019 年 7 月经手术切除 102 例胃癌组织蜡块标本的患者作为观察组,另随机抽取胃癌患者标本切缘的癌旁组织 60 例作为对照组。比较 CEA、AEP 在胃癌组织和癌旁组织的关系,且记录与临床病理参数之间的关系。**结果:**在胃癌组织中 CEA、AEP 的阳性表达率明显比癌旁组织高[47.06%(48/102)比 3.33%(2/60),55.88%(57/102)比 1.67%(1/60)],差异有统计学意义($P<0.05$);CEA、AEP 和肿瘤大小、TNM 分期、淋巴结转移、不同浸润程度、不同分化程度之间比较,差异有统计学意义($P<0.05$);经 Spearman 相关性分析结果显示,胃癌组织中 CEA、AEP 和肿瘤大小、分化程度、TNM 分期、淋巴结转移、浸润程度之间均呈正相关($P<0.05$);经 Pearson 相关分析显示,在胃癌组织中 CEA、AEP 的表达均呈现正相关($r=0.217, P=0.010$)。**结论:**CEA、AEP 在胃癌患者组织中有明显高表达,和临床病理特征有明显相关性,且两者有相互协同效应,本研究也为胃癌预后判断、靶向治疗等提供了一定依据。

关键词:胃癌;T 淋巴细胞亚群;凝血功能;癌胚抗原;天冬酰胺内肽酶

中图分类号:R735.2 文献标识码:A 文章编号:1673-6273(2020)09-1783-05

Expression and Correlation Analysis of CEA and AEP in Patients with Gastric Cancer*

LU Shu-juan¹, ZHANG Xiao-yan¹, GUAN Jia-nan², SUN Xiao³, ZHANG Jun-jie³

(1 Department of Pathology; 2 Department of Oncology, The Fifth People's Hospital of Shenyang, Shenyang, Liaoning, 110023, China;

3 Department of Pathology, Affiliated Central Hospital of Shenyang Medical College, Shenyang, Liaoning, 110024, China)

ABSTRACT Objective: To study expression and correlation analysis of carcinoembryonic antigen (CEA) and asparagine endopeptidase (AEP) in gastric cancer patients. **Methods:** A retrospective analysis was made on 102 patients with gastric cancer tissue wax samples surgically removed from September 2016 to July 2019 as the observation group, and 60 adjacent tissues in the margin of gastric cancer were randomly selected as the control group. The relationship between CEA, AEP and clinicopathological parameters was compared in gastric cancer group and adjacent tissues. **Results:** The positive expression rate of CEA and AEP in gastric cancer was significantly higher than that in adjacent tissues [47.06%(48/102) vs 3.33%(2/60), 55.88%(57/102) vs 1.67%(1/60)], the difference has statistically significant ($P<0.05$); CEA, AEP and tumor size, TNM stage, lymph node metastasis, different degree of infiltration, the difference has statistically significant ($P<0.05$); the Spearman correlation analysis showed that there was a positive correlation between CEA, AEP and tumor size, degree of differentiation, TNM stage, lymph node metastasis, and degree of invasion in gastric cancer tissues ($P<0.05$); the Pearson correlation analysis showed that CEA and AEP were positively correlated in gastric cancer ($r=0.217, P=0.010$). **Conclusion:** The CEA and AEP are highly expressed in gastric cancer tissues, which have obvious correlation with clinicopathological features, and they have synergistic effect. This study also provides a certain basis for prognosis judgment and targeted treatment of gastric cancer.

Key words: Gastric cancer; T lymphocyte subsets; Coagulation function; Carcinoembryonic antigen; Asparagine endopeptidase

Chinese Library Classification(CLC): R735.2 **Document code:** A

Article ID: 1673-6273(2020)09-1783-05

前言

胃癌在临床上是种十分常见的恶性肿瘤之一,该病具有临床症状晚、进展速度快、生存率低的特点,其死亡率在世界位居第二,且发病率有逐年增长的走势^[1,2]。随着对胃癌中分子学机制的研究,以及对肿瘤细胞转移、增殖生长过程中的信号转到通路作用机制的不断深入了解,逐渐认识到该病在发生和发

展过程中涉及到多个基因和分子的表达和水平变化^[3,4]。癌胚抗原(CEA)广泛存在于内胚层及部分非内胚层的恶性肿瘤组织中细胞表面的结构蛋白,是癌胚抗原和肿瘤标志物,可以辅助诊断癌症,但并不具有特异性。有研究发现,CEA 对消化道肿瘤的敏感度相对比较高,CEA 可以判断患者术后是否会复发,值越大,说明癌症复发的概率越大^[5,6]。在近年来的研究中发现,天冬酰胺内肽酶(AEP),是切割天冬酰胺残基 C-末端的肽键

* 基金项目:辽宁省自然科学基金项目(2018102254)

作者简介:芦淑娟(1965-),女,本科,副主任医师,研究方向:消化道肿瘤,电话:15998842399, E-mail:vtgffo@163.com

(收稿日期:2020-01-06 接受日期:2020-01-30)

的溶酶体半胱氨酸蛋白酶,目前国外有研究指出,AEP在结肠癌、乳腺癌等实体肿瘤中高表达,与肿瘤的转移、扩散、侵袭等行为密切相关^[7,8]。因此,本次研究旨在探讨胃癌患者组织中CEA、AEP的表达及相关性分析。

1 资料与方法

1.1 一般资料

回顾性分析2016年9月至2019年7月于经手术切除102例胃癌组织蜡块标本的患者作为观察组,均通过术后病理组织学检查确诊为胃癌^[9,10]。

纳入标准:1.实验室检查早期可疑胃癌,游离胃酸低度或缺,如红血球压积、血红蛋白、红细胞下降,水电解质紊乱,酸碱平衡失调等化验异常;2.体征早期无特殊体征,晚期可见上腹肿块,直肠指诊可及肿块,左锁骨上淋巴结肿大,同时贫血、消瘦、腹水等恶液质表现;3.症状早期表现为上腹不适,约为

80%患者有此表现,将近50%胃癌患者有明显食欲减退或食欲不振。晚期可出现乏力,腰背疼及梗阻后出现恶心、呕吐、进食困难。肿瘤表面溃疡时出现呕血、黑便;4.X线表现气钡双重造影可清楚显示胃轮廓、蠕动情况、粘膜形态、排空时间,有无充盈缺损、龛影等5.内镜检查胃息肉长度>2cm。排除标准:1.心肝肾重要器官功能不全;2.术前均未接受过放化疗;3.合并其他恶性肿瘤;4.心脑血管系统疾病。患者均采用国际抗癌联盟的TNM分期,T代表原发灶侵犯的范围,N是指淋巴结转移的情况,M是指是否存在远处脏器的转移,TNM分期是比较准确的反映一个肿瘤的早、中、晚期的级别,一般为:I期、II期、III期、IV期。在102例胃癌组织蜡块标本的患者中随机抽取胃癌患者标本切缘的癌旁组织60例作为对照组,两组一般资料见表1,差异无统计学意义($P>0.05$)。本研究已通过我院伦理委员会批准实施。

表1 两组一般资料比较 $[\bar{x}\pm s, n(\%)]$

Table 1 Comparison of general data between two groups $[\bar{x}\pm s, n(\%)]$

Groups	Man	Women	BMI(kg/m ²)	Age(year)	Course of disease(year)
Observation group (n=102)	65(63.73)	37(36.27)	26.70 $\pm$ 2.16	66.51 $\pm$ 1.26	4.20 $\pm$ 1.24
Control group(n=60)	35(58.33)	25(41.67)	26.68 $\pm$ 2.20	67.40 $\pm$ 1.38	4.18 $\pm$ 1.26

1.2 方法

试剂:鼠抗人CEA单克隆抗体,购自武汉艾美捷科技有限公司,鼠抗人AEP单克隆抗体,购自北京华夏远洋科技有限公司。DAB显色试剂盒均购于武汉博士德生物工程有限公司。

将所收集的标本使用浓度为10%福尔马林溶液进行固定,常规石蜡包埋,并进行4 μ m连续切片,予以储存,使用免疫组织化学染色法对组织切片进行染色,使用PBS作为阳性对照,CEA、AEP的阳性判定标准^[11]:均以细胞膜、胞质内有黄色、棕褐色颗粒阳性着色出现,根据阳性着色程度记录分数,0分为无着色,颜色和背景色一样,1分呈浅黄色,颜色略深于背景色,2分呈棕黄色,颜色比背景色明显更深,3分呈棕褐色,并记录阳性细胞所占比例的评分,0分为阴性,1分为比例<10%,2分为比例11%~50%,3分为比例51%~75%,4分为比例>

75%;根据着色程度评分和阳性细胞所占比例的评分,阴性为0~2分,弱阳性为3~4分,中度阳性为5~8分,强阳性为9~12分,其中弱阳性、中度阳性、强阳性判定为阳性表达。

1.3 统计学分析

以spss18.0软件包处理,计量资料用 $(\bar{x}\pm s)$ 表示,组间比较使用独立样本t检验,计数资料以率表示, χ^2 检验,CEA、AEP的相关性分析使用Spearman等级分析, $P<0.05$ 表示差异具有统计学意义。

2 结果

2.1 胃癌组织与癌旁组织中CEA、AEP表达比较

在胃癌组织中CEA、AEP的阳性表达率明显比癌旁组织高,差异有统计学意义($P<0.05$),见表2。

表2 胃癌组织与癌旁组织中CEA、AEP表达比较(例,%)

Table 2 Expression of CEA and AEP in gastric cancer and paracancerous tissues(n, %)

Groups	CEA	AEP
Observation group(n=102)	48(47.06)	57(55.88)
Control group(n=60)	0(0.00)*	1(1.67)*

Note: Compared with the observation group, * $P<0.05$.

2.2 胃癌组织中CEA、AEP和临床病理参数的关系

CEA、AEP和性别、年龄之间差异无统计学意义($P>0.05$),在不同肿瘤大小、TNM分期、淋巴结转移、浸润程度、分化程度患者中,CEA、AEP的阳性率表达,差异有统计学意义($P<0.05$),见表3。

2.3 胃癌组织中CEA、AEP和胃癌患者临床病理特征的相关性分析

将肿瘤大小、分化程度、TNM分期、淋巴结转移、浸润程度作为因变量,将胃癌组织中CEA、AEP作为自变量,经Spearman相关性分析结果显示,胃癌组织中CEA、AEP和肿瘤大小、分化程度、TNM分期、淋巴结转移、浸润程度之间均呈正相关($P<0.05$),见表4。

2.4 胃癌组织中CEA、AEP相关性分析

经Pearson相关分析显示,在胃癌组织中CEA、AEP的表

表 3 胃癌组织中 CEA、AEP 和临床病理参数的关系(例,%)
Table 3 Relationship between CEA, AEP and clinicopathological parameters in gastric cancer (example, %)

Project		Number of cases	CEA	AEP
			Positive rate	
Gender	Man	70	34(48.57)	46(65.71)
	Woman	32	14(43.75)	11(34.38)
Age	≥ 60 years	40	12(30.00)	27(67.50)
	< 60 years	62	36(58.06)	30(48.39)
Tumour size	< 5 cm	75	22(1.33)	36(58.00)
	≥ 5 cm	27	26(96.30)	21(77.78)
TNM stages	I+II	40	13(32.50)	17(42.50)
	III+IV	62	35(56.45)	40(64.52)
Lymph node metastasis	Have	66	44(66.67)	51(77.27)
	No	36	4(11.11)	6(16.67)
Infiltration degree	Mucosal layer, submucosa, muscular layer	34	8(23.53)	12(35.29)
	Serous and extraserous	68	40(58.82)	45(66.18)
Degree of differentiation	High and medium differentiation	44	15(34.09)	20(34.48)
	Low, undifferentiated	58	33(56.90)	37(63.79)*

表 4 胃癌组织中 CEA、AEP 和胃癌患者临床病理特征的相关性分析
Table 4 Correlation Analysis of CEA, AEP and clinicopathological characteristics of gastric cancer

Clinical pathology	CXCL5		TGFβ1	
	r	P	r	P
Tumor size	0.410	<0.01	0.617	<0.01
Degree of differentiation	0.567	<0.01	0.548	<0.01
TNM staging	0.495	<0.01	0.470	<0.01
Lymph node metastasis	0.668	<0.01	0.592	<0.01
Infiltration degree	0.423	<0.01	0.505	<0.01

达均呈现正相关($r=0.217, P=0.010$), 图 1。
胃癌属于临床恶性肿瘤中常见的一种, 其中淋巴结转移和浸润是影响胃癌治疗的关键因素, 也是致死率的主要原因^[12]。

3 讨论

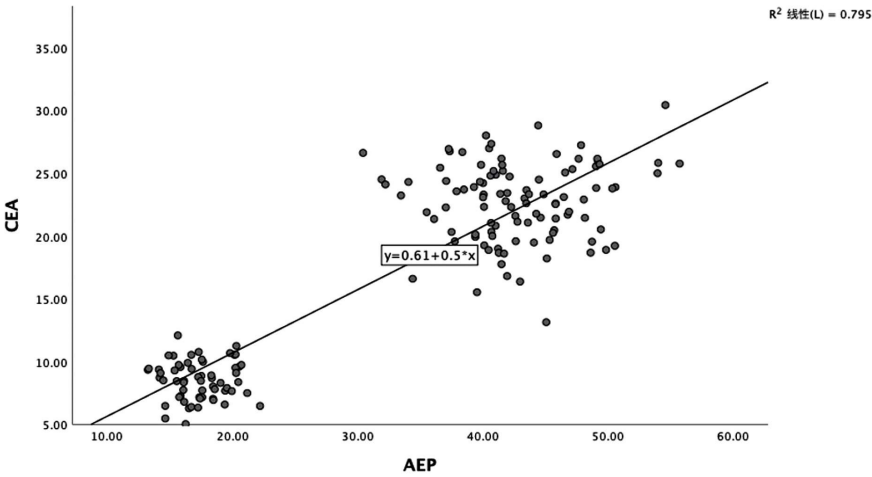


图 1 胃癌组织中 CEA、AEP 的相关性散点图

Fig.1 Correlation scatter diagram of CEA and AEP in gastric cancer tissue

主要的致病因素有:亚硝酸盐化合物,HP感染,饮食因素,遗传因素^[13,14]。目前每年全球胃癌患者患病率有逐年递增的趋势,严重危害患者身体健康^[15,16]。胃癌的治疗措施主要有姑息性手术治疗、化学治疗、放射治疗^[17,18]。内镜黏膜下剥离术已在早期胃癌患者中取得了满意的疗效,但术后仍有复发现象,不利于预后^[19]。分子靶向治疗属于肿瘤研究领域的热点,通过有效、针对性的分子靶向治疗手段,在挽救胃癌患者预后中十分重要^[19,20]。

胃癌通过降解基底膜、细胞外基质等作用再由内向外进行扩散,并在邻近组织、远处器官等部位出现浸润、转移现象,加速疾病进展^[21,22]。CEA是在人体的消化道、肝脏、胰腺中合成,随着身体的成长其指标水平呈下降的趋势,但在患者患癌后这项指标又出现升高。这项指标对于内胚层组织的恶性肿瘤,如胰腺、肝脏、肺脏、结直肠癌的阳性率是非常高的^[23]。目前已被证实其在胃癌的治疗监视、癌前病变的检测的中具有重要的价值,敏感度较高,有助于早期诊断、治疗及评估疾病预后^[24,25]。但也有较多学者认为,癌细胞在增值的过程中涉及到不同生长因子、信号通路的参加,单独检测一个因子所得到的结论有一定的片面性,而进行联合分析在指导临床应用中具有着重要作用^[26,27]。

肿瘤细胞具有快速增殖的特性,需要生物大分子提供能量和生物合成,以实现不断增殖的需求,AEP是一种溶酶体半胱氨酸内肽酶,能够特异性水解天冬酰胺残基羧基端肽键,也能够对天冬氨酸残基羧基端肽键进行水解^[28]。AE基因的组成主要包括433个氨基酸残基所组成,带有一个信号肽,结构十分稳定,近年来已有较多研究发现,其与肿瘤的转移、扩散、侵袭等行为密切相关^[29,30]。目前的实验中,AEP已被证实在乳腺癌、结肠癌、前列腺癌等诸多实体瘤中均呈现着高表达,参与着肿瘤血管的形成、肿瘤浸润转移等过程^[31]。

本研究结果显示,胃癌组织中CEA、AEP阳性表达明显比癌旁组织更高,且和肿瘤大小、TNM分期、淋巴结转移、不同浸润程度、不同分化程度之间具有密切联系,疾病严重程度越高,阳性表达率也就越高,通过分析可能是由于AEP是一种应激反应蛋白,可在特定的条件下生成,在胃癌患者中,存在着明显环境压力,例如缺氧等,可造成AEP出现高表达^[32]。有研究也显示,ATP在黑素瘤肿瘤环境中改变了抗癌细胞和调节性T细胞之间的平衡关键。这些发现表明,在没有AEP的情况下,检查点抑制剂可能没有有益的反应,并且在用检查点抑制剂治疗之前测量患者中的AEP蛋白水平可以为癌症免疫治疗方案提供更好的响应率^[33,34]。AEP对基质金属蛋白酶-2的表达具有激活作用,并通过该途径对肿瘤细胞侵袭、浸润等产生影响^[35]。此外,在本次研究经Spearman相关性分析结果显示,胃癌组织中CEA、AEP和肿瘤大小、分化程度、TNM分期、淋巴结转移、浸润程度之间均呈正相关;经Pearson相关分析显示,在胃癌组织中CEA、AEP的表达均呈现正相关,两者在癌症生物学方面可能存在着联系,提示表明它们在胃癌的发生、发展过程中存在着相互协同的作用,CEA、AEP与胃癌之间的关系临床上仍需要作进一步的研究。

综上所述,CEA、AEP在胃癌患者组织中有明显高表达,和

临床病理特征有明显相关性,且两者有相互协同效应,本研究也为胃癌预后判断、靶向治疗等提供了一定依据。

参考文献(References)

- [1] Xingya Zhu, Mengmeng Lv, Hao Wang, et al. Identification of Circulating MicroRNAs as Novel Potential Biomarkers for Gastric Cancer Detection: A Systematic Review and Meta-Analysis [J]. Digestive Diseases and Sciences, 2014, 59(5): 911-919
- [2] Omar Abdel-Rahman. Immune checkpoints aberrations and gastric cancer; assessment of prognostic value and evaluation of therapeutic potentials [J]. Critical reviews in oncology/hematology, 2015, 97(9): 65-71
- [3] Venerito, Marino, Link, Alexander, Rokkas, Theodoros, et al. Gastric cancer clinical and epidemiological aspects[J]. Helicobacter, 2016, 21(S1): 39-44
- [4] Keishiro Aoyagi, Kikuo Kouhiji, Junya Kizaki, et al. Molecular targeting to treat gastric cancer[J]. World Journal of Gastroenterology, 2014, 20(38): 13741-13755
- [5] Petra Hudler. Challenges of deciphering gastric cancer heterogeneity [J]. World Journal of Gastroenterology, 2015, 21(37): 10510
- [6] Jin-Lian Chen, Jing Fan, Xiao-jie Lu. CE-MS based on moving reaction boundary method for urinary metabolomic analysis of gastric cancer patients[J]. Electrophoresis, 2014, 35(7): 1032-1039
- [7] Rui Zhao, Yanli Zhang, Xin Zhang, et al. Exosomal long noncoding RNA HOTTIP as potential novel diagnostic and prognostic biomarker test for gastric cancer[J]. Molecular Cancer, 2018, 17(1): 68
- [8] Byung Joon Choi, Jung Hwan Yoon, Olga Kim, et al. Influence of the h TERT rs2736100 polymorphism on telomere length in gastric cancer[J]. World Journal of Gastroenterology, 2015, 21(31): 9328-9236
- [9] E Yeldan, S Oguz, U Usta, et al. Risk factors for peritoneal dissemination of gastric cancer [J]. Minerva chirurgica, 2015, 70(2): 91-96
- [10] Se Woo Park, Hang Lak Lee, Yong Won Ju, et al. Inverse Association Between Visceral Obesity and Lymph Node Metastasis in Gastric Cancer[J]. Journal of Gastrointestinal Surgery, 2015, 19(2): 242-250
- [11] Taisuke Imamura, Shuhei Komatsu, Daisuke Ichikawa, et al. Clinical characteristics of hepatoduodenal lymph node metastasis in gastric cancer[J]. World Journal of Gastroenterology, 2015, 21(38): 10866-10873
- [12] Shing Leng Chan, Jimmy B. Y. So. Gastric Cancer Therapy [M]. Encyclopedia of Cancer, 2016
- [13] Lauren Peirce Carcas. Gastric cancer review [J]. Journal of Carcinogenesis, 2014, 13(1): 14
- [14] Allgayer H, Heiss MM, Schildberg FW. Prognostic factors in gastric cancer[J]. The British Journal of Surgery, 2015, 61(2): 67-70
- [15] Rintaro Hashimoto, Hidetaka Hamamoto, Yuko Omori, et al. Early gastric cancer on submucosal heterotopic gastric glands [J]. Gastrointestinal endoscopy, 2016, 85(4): 851-852
- [16] Takuto Suzuki, Yoshiyasu Kitagawa, Rino Nankinzan, et al. Early gastric cancer diagnostic ability of ultrathin endoscope loaded with laser light source[J]. World Journal of Gastroenterology, 2019, 25(11): 1378-1386
- [17] Shujing Xia, Lili Zhang, Fenggan Cheng, et al. Expression of PSMA

- 7 and its effect on proliferation, invasion, migration and tumorigenesis of gastric cancer[J]. Journal of Southern Medical University, 2019, 39(4): 387-393
- [18] Tomoyuki Irino, Hiroya Takeuchi, Masanori Terashima, et al. Gastric Cancer in Asia: Unique Features and Management [J]. American Society of Clinical Oncology Educational Book, 2017, 37: 279-291
- [19] V. Marek, R. Zahorec, J. Palaj, et al. Gastric cancer with liver metastasis[J]. Bratislavské Lekárske Listy, 2016, 117(1): 59
- [20] Ondřej Daum, Magdaléna Dubová, Alena Skálová, et al. Predictive diagnostics of gastric cancer in 2018 [J]. Ceskoslovenska patologie, 2018, 54(1): 23-26
- [21] Samantha Morais, Clara Castro, Luís Antunes, et al. Second primary cancers and survival in patients with gastric cancer: association with prediagnosis lifestyles[J]. European Journal of Cancer Prevention, 2018, 28(3): 1
- [22] Shu-Bo Tian, Jian-Chun Yu, Wei-Ming Kang, et al. Combined Detection of CEA, CA 19-9, CA 242 and CA 50 in the Diagnosis and Prognosis of Resectable Gastric Cancer [J]. Asian Pacific journal of cancer prevention: APJCP, 2014, 15(15): 6295-6300
- [23] Kazuhiro Matsueda, Toshio Otani, Yusuke Fujioka, et al. A giant apocrine hidrocystoma associated with elevated serum carcinoembryonic antigen levels: a case report[J]. Journal of Medical Case Reports, 2019, 13(1): 237
- [24] Zhen Li, Dewei Zhang, Hao Zhang, et al. Prediction of peritoneal recurrence by the mRNA level of CEA and MMP-7 in peritoneal lavage of gastric cancer patients[J]. Tumor Biology, 2014, 35(4): 3463-3470
- [25] Noriko Wada, Yukinori Kurokawa, Yasuhiro Miyazaki, et al. The characteristics of the serum carcinoembryonic antigen and carbohydrate antigen 19-9 levels in gastric cancer cases [J]. Surgery Today, 2016, 47(2): 1-6
- [26] Changguo Chen, Qiuyuan Chen, Qiangyuan Zhao, et al. Value of combined detection of serum CEA, CA72-4, CA19-9, CA15-3 and CA12-5 in the diagnosis of gastric cancer[J]. Annals of clinical and laboratory science, 2017, 47(3): 260-263
- [27] Lu Wang, Wen-Jing Yang. Effect of taxanes combined with platinum chemotherapy on serum HE4, AFP, DDX4, CD133, CEA and T lymphocyte subsets in patients with epithelial ovarian cancer [J]. Journal of Hainan Medical University, 2016, 22(18): 91-94
- [28] Takeshi Setoyama, Shin'ichi Miyamoto, Mitsuhiro Nikaido, et al. New Perspectives in Gastric Cancer: Helicobacter pylori-Uninfected Pure Signet Ring Cell Carcinoma [M]. Alcoholic/Non-Alcoholic Digestive Diseases, 2019
- [29] A. Husaiyin, A. Abulimiti, W.-B. Zhang, et al. Effect of laparoscopic surgery on levels of immune cells and coagulation function in patients with gastric cancer [J]. World Chinese Journal of Digestology, 2016, 14(11): 761-767
- [30] Gurzu, Simona, Kadar, Zoltan, Sugimura, Haruhiko, et al. Maspin-related Orchestration of Aggressiveness of Gastric Cancer[J]. Applied Immunohistochemistry & Molecular Morphology, 2016, 24(5): 326
- [31] Hadas Pahima, Simona Reina, Noa Tadmor, et al. Hypoxic-induced truncation of voltage-dependent anion channel 1 is mediated by both asparagine endopeptidase and calpain 1 activities [J]. Oncotarget, 2018, 9(16): 12825-12841
- [32] G B Baretton, D E Aust. Current biomarkers for gastric cancer[J]. Der Pathologe, 2017, 38(2): 1-5
- [33] Jian Li, Liang Xu, Zeng-Ci Run, et al. Multiple cytokine profiling in serum for early detection of gastric cancer [J]. World Journal of Gastroenterology, 2018, 24(21): 2269-2278
- [34] Peiming Zheng, Qin Luo, Weiwei Wang, et al. Tumor-associated macrophages-derived exosomes promote the migration of gastric cancer cells by transfer of functional Apolipoprotein E[J]. Cell Death & Disease, 2018, 9(4): 434
- [35] Cui Y, Wang Y, Li H, et al. Asparaginyl endopeptidase promotes the invasion and metastasis of gastric cancer through modulating epithelial-to-mesenchymal transition[J]. Oncotarget, 2016, 7(23): 34356-34370

(上接第 1760 页)

- [25] Larco J E D, Wuertz B R K, Rosner K A, et al. A Potential Role for Interleukin-8 in the Metastatic Phenotype of Breast Carcinoma Cells [J]. Am J Pathol, 2001, 158(2): 639-646
- [26] Solomon P, Dong Y, Dogra S, et al. Interleukin 8 is a biomarker of telomerase inhibition in cancer cells[J]. BMC Cancer, 2018, 18(1): 730
- [27] Urquidi V, Chang M, Dai Y, et al. IL-8 as a urinary biomarker for the detection of bladder cancer[J]. BMC Urol, 2012, 12(1): 12
- [28] Nahi Yousif Yaseen, Issam Salman Al-Azzawi, Maysoon Ali Saleem, et al. Urinary IL-8 and BLCA-4 in detection of bladder cancer and their clinical significant [J]. Iraqi Journal of Cancer and Medical Genetics, 2015, 8(1): 31-45
- [29] 汤志灵, 唐晨野, 莫娟芬, 等. 基质金属蛋白酶表达在膀胱癌侵袭转移中的作用[J]. 中国基层医药, 2018, 25(2): 156-160
- [30] Wang Z, Li H, Qiang C, et al. Clinical Significance of Serological and Urological Levels of Bladder Cancer-Specific Antigen-1 (BLCA-1) in Bladder Cancer [J]. Medical Science Monitor International Medical Journal of Experimental & Clinical Research, 2018, 24: 3882-3887
- [31] Sizemore G M, Pitarresi J R, Balakrishnan S, et al. The ETS family of oncogenic transcription factors in solid tumours [J]. Nat Rev Cancer, 2017, 17(6): 337-351