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· 论著 ·

# 组织蛋白酶 B 在鼻咽癌患者组织和血清中的表达及临床意义

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**摘要:** **目的** 通过测定组织蛋白酶 B(Capthesin B)在鼻咽癌组织和血清标本中的表达量,探讨 Capthesin B 作为评估鼻咽癌患者治疗预后的可行性。**方法** 收集长沙金域医学检验中心 2019 年 8 月—2020 年 2 月 50 例鼻咽癌组织和癌旁正常组织标本,免疫组织化学(IHC)检测组织标本 Capthesin B 表达,比较分析蛋白表达差异。收集湖南省肿瘤医院 2019 年 7 月—2020 年 3 月 106 例鼻咽癌患者治疗前、治疗后及 40 例健康体检者的血清标本,ELISA 试验检测血清 Capthesin B 浓度,并比较分析 3 组间的血清 Capthesin B 浓度。**结果** IHC 结果显示,鼻咽癌组织 Capthesin B 阳性率显著高于癌旁正常组织( $P < 0.001$ )。ELISA 结果表明,鼻咽癌患者血清 Capthesin B  $1.23 (0.64, 2.27)$  ng/mL 显著高于健康体检组的  $(0.98 \pm 0.49)$  ng/mL( $P < 0.05$ ),鼻咽癌患者治疗后血清 Capthesin B  $0.69 (0.39, 1.42)$  ng/mL 显著低于治疗前的  $1.23 (0.64, 2.27)$  ng/mL( $P < 0.001$ )。TNM 分期 III、IV 患者血清 Capthesin B  $(2.09 \pm 1.50)$  ng/mL 显著高于 I、II 期患者的  $1.14 (0.60, 2.12)$  ng/mL,提示 Capthesin B 水平与 TNM 分期显著相关( $P < 0.05$ )。鼻咽癌颈淋巴结转移组血清 Capthesin B  $(2.63 \pm 1.67)$  ng/mL 显著高于未转移组的  $1.10 (0.59, 2.14)$  ng/mL( $P < 0.01$ ),提示 Capthesin B 与转移相关。工作特征(ROC)曲线下面积(AUC)为  $0.670 (P < 0.001)$ ,提示血清 Capthesin B 可作为鼻咽癌疗效预测的参考指标。**结论** 鼻咽癌组织 Capthesin B 高表达和患者血清 Capthesin B 浓度明显升高,治疗后其浓度降低,提示 Capthesin B 与鼻咽癌发生发展密切相关。Capthesin B 与肿瘤淋巴结转移及 TNM 分期呈正相关,提示 Capthesin B 可作为鼻咽癌治疗预后的参考指标。

**关键词:**鼻咽癌;组织蛋白酶 B;生物标志物;预后

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## Expression of cathepsin B and its clinical significance in tissues and serum of nasopharyngeal carcinoma

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**Abstract:** **Objective** The study investigates the feasibility of Capthesin B as a marker for evaluating the therapeutic efficiency of nasopharyngeal carcinoma (NPC) patients through detecting the expression of Capthesin B in NPC tissues and serum. **Methods** The tumor and adjacent normal tissue samples from 50 NPC patients were obtained through biopsy. Immunohistochemistry (IHC) was used to detect the expression of Capthesin B in the tissues of these samples, which were collected in Changsha Jinyu Medical Laboratory Center from August 2019 to February 2020. Serum samples from 40 healthy subjects and from 106 patients with NPC before and after treatment were collected in Hunan Cancer Hospital from July 2019 to March 2020. Capthesin B in the serum was detected by ELISA, and the serum concentrations of Capthesin B among the three groups were compared and analyzed. **Results** IHC results showed that the positive rate of Capthesin B in NPC tissues was significantly higher than that in adjacent tissues ( $P < 0.01$ ). ELISA data showed that the serum level of Capthesin B in nasopharyngeal carcinoma patients  $1.23 (0.64, 2.27)$  ng/mL was significantly higher than that in healthy subjects  $(0.98 \pm$

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0.49) ng/mL ( $P < 0.01$ ). The serum Capthesin B of NPC patients after treatment 0.69 (0.39, 1.42) ng/mL was significantly lower than that before treatment 1.23 (0.64, 2.27) ng/mL ( $P < 0.001$ ). The area under the ROC curve (AUC) was 0.670 ( $P < 0.05$ ), which suggested that Capthesin B may be used as a reference for predicting the therapeutic efficiency of NPC. The serum Capthesin B of TNM stage III, IV NPC patients ( $2.09 \pm 1.50$ ) ng/mL was significantly higher than that of TNM stage I, II NPC patients 1.14 (0.60, 2.12) ng/mL, which indicated that Capthesin B was significantly correlated with TNM stage ( $P < 0.05$ ). Serum Capthesin B in the metastatic group ( $2.63 \pm 1.67$ ) ng/mL was remarkably higher than that in the non-metastatic group 1.10 (0.59, 2.14) ng/mL ( $P < 0.01$ ), which suggested that serum Capthesin B may be used as a biomarker for predicting NPC metastasis. **Conclusion** The level of Capthesin B expression in NPC tissues and in NPC serum were significantly increased, but decreased after treatment of NPC, which suggested that Capthesin B is closely related to NPC development. Capthesin B was positively correlated with lymph node metastasis and TNM stage, which suggested that Capthesin B could be used as a biomarker for evaluating NPC prognosis.

**Keywords:** Nasopharyngeal carcinoma; Capthesin B; Biomarker; Prognosis

鼻咽癌是我国南方及东南亚地区一种常见的头颈恶性肿瘤,其起源于鼻咽部上皮细胞。我国华南地区广东、广西和湖南发病率极高<sup>[1]</sup>。研究表明,鼻咽癌的发病不仅与EBV病毒(Epstein-Barr virus, EBV)感染、化学致癌物和环境暴露有关,而且与基因的遗传性突变密切相关<sup>[1]</sup>。流行病学调查显示,鼻咽癌发病具有显著的种族差异、遗传易感性及家族聚集性<sup>[2]</sup>。远处转移和高度侵袭是鼻咽癌较为显著的临床特征,也是导致患者治疗疗效不佳、生存率降低的重要因素<sup>[3]</sup>。

组织蛋白酶(Capthesins)是一类溶酶体半胱氨酸组织蛋白酶,包括11个家族成员(Cathepsin B、C、F等),这些溶酶体组织蛋白酶可消化清除胞内异物,在维持细胞内环境稳定方面发挥重要功能<sup>[4]</sup>。Capthesin B是Capthesins家族的重要成员,在溶酶体级联反应中发挥关键作用。Capthesin B以主转录本、缺少外显子2主转录本及缺少外显子2和3主转录本等3个形式存在<sup>[5]</sup>。研究发现, Capthesin B位于癌基因突变的肿瘤细胞表面,例如MCF10AneoT乳腺癌上皮细胞<sup>[6]</sup>、B16黑素瘤细胞<sup>[7]</sup>、HCT 116结肠癌细胞<sup>[8]</sup>。Capthesin B与肿瘤细胞表面膜联蛋白II异四聚体的轻链结合,定位于肿瘤细胞膜的微泡中<sup>[9]</sup>,肿瘤细胞可通过膜泡、微泡或脱落外泌体分泌活性Capthesin B<sup>[10]</sup>。

临床研究发现 Capthesin B在多种癌症中过表达,如乳腺癌<sup>[11]</sup>、结直肠癌<sup>[8]</sup>、前列腺癌<sup>[12]</sup>、口腔癌<sup>[13]</sup>、脑癌<sup>[14]</sup>、肝癌<sup>[15]</sup>、鼻咽癌<sup>[16]</sup>和肺癌<sup>[17]</sup>。Capthesin B通过调节细胞分化、肿瘤细胞生长、自噬、凋亡、迁移、侵袭、血管生成、细胞外基质(ECM)重构及肿瘤免疫反应,参与癌症的发生发展<sup>[18]</sup>。Capthesin B过表达与鼻咽癌的侵袭和转移有关<sup>[19]</sup>。为探讨 Capthesin B是否可以作为鼻咽癌治疗预后

的评估指标,本研究检测了鼻咽癌患者和健康体检者血清标本的 Capthesin B浓度,同时还检测了鼻咽癌组织和癌旁正常组织标本 Capthesin B表达,结合临床资料分析 Capthesin B与鼻咽癌发生发展、治疗预后的关系。

## 1 材料与方法

### 1.1 试剂和抗体

Capthesin B抗体(12216-1-AP)购自武汉三鹰生物技术有限公司, Capthesin B酶联免疫吸附试验(ELISA)试剂盒(CSTB, CSB-E13450h)购自武汉华美生物工程有限公司,免疫组织化学染色(IHC)试剂盒 SP Rabbit & Mouse HRP Kit(CW2069)购自北京康为世纪生物科技有限公司。

### 1.2 鼻咽癌患者血清及组织标本

收集长沙金域医学检验中心2019年8月—2020年2月50例鼻咽癌原发及癌旁正常组织标本,所有患者均经病理学确诊为鼻咽癌,其中男33例,女17例;年龄29~76岁,中位年龄为43.5岁;低分化鳞癌27例,中分化鳞癌19例,高分化鳞癌4例;颈淋巴结转移7例。收集湖南省肿瘤医院检验科2019年7月—2020年3月106例病理学确诊为鼻咽癌患者治疗前、治疗后的血清标本及临床资料,包括年龄、性别、EBVCA-IgG、EBVEA-IgA和TNM分期等。106例鼻咽癌患者中男83例,女23例;年龄27~78岁,平均年龄( $50.8 \pm 12.1$ )岁;平均治疗时间1.00(0.70, 3.00)个月;低分化鳞癌96例,中分化鳞癌8例,高分化鳞癌2例;颈淋巴结转移16例。同期收集40例健康体检者的血清标本及临床资料,其中男22例,女18例;年龄25~68岁,中位年龄为42岁。本研究经湖南省肿瘤医

院伦理委员会评审通过。

### 1.3 Capthesin B IHC 分析

根据试剂盒的操作说明书进行 Capthesin B IHC 分析。鼻咽癌组织切片脱蜡至水;抗原热修复;内源性酶灭活;加一抗(Ab-cathepsin B)孵育;加二抗孵育;DAB 显色;苏木素复染;PBS 返蓝;中性树胶封片、显微镜观察。细胞核/细胞质染色呈黄色或棕黄色(颜色深时为棕色),认为靶蛋白呈阳性,阳性程度用光密度平均值表示[光密度平均值 = 累积光密度( IOD)/视野面积( Area) ]。

### 1.4 鼻咽癌组织苏木精伊红染色( HE)

按常规组织染色进行鼻咽癌组织 HE 染色。即组织切片脱蜡至水,苏木素染液染色,PBS 返蓝,伊红染复染,乙醇( 95% ~ 100%) 脱水,二甲苯浸泡,2 次,中性树胶封片,显微镜观察。

### 1.5 ELISA

ELISA 方法检测鼻咽癌血清 Capthesin B,具体操作按 ELISA 试剂盒操作说明进行。将标准品倍比稀释,每孔分别加标准品或待测样本,37℃ 温育 30 min,洗板后每孔加辣根过氧化物酶标记物工作液 100  $\mu$ L,37℃ 温育 30 min;洗板后加底物溶液 90  $\mu$ L,37℃ 避光显色 20 min;加终止液终止反应;用酶标仪在 450 m 波长依序测量各孔的光密度( OD 值)。根据标准品的浓度与 OD 值计算标准曲线,计算样本浓度,颜色深度与样品浓度成正比。

### 1.6 统计学分析

采用 SPSS 21.0 和 GraphPad Prism 7.0 软件进行统计学分析。符合正态分布的数值用  $\bar{x} \pm s$  描述变量的分布情况;不符合正态分布的数值用中位数(上四分位数,下四分位数)[  $Q_2(Q_1, Q_3)$  ]描述变量的分布情况。组间差异采用 Mann-Whitney  $U$  检验进行统计学检验。以中位数作为指标的临界值,进行受试者工作特征( ROC) 曲线分析。以  $P < 0.05$  为差异具有统计学意义。

## 2 结果

### 2.1 人鼻咽癌组织中 Capthesin B 表达

IHC 结果显示,鼻咽癌组织中 Capthesin B 阳性率明显高于癌旁正常组织( $P < 0.001$ )。TNM 分期为 III、IV 期、中低分化、有颈淋巴结转移鼻咽癌组织中 Capthesin B 阳性率明显高于 TNM 分期为 I、II 期、高分化、无颈淋巴结转移者( $P < 0.05$ ),不同性别、年龄鼻咽癌组织中 Capthesin B 阳性率比较无

统计学差异( $P > 0.05$ ),见图 1、表 1。

表 1 鼻咽癌患者组织 Capthesin B 阳性率与临床特征的相关性分析 [  $Q_2(Q_1, Q_3)$  ]

临床指标	例数	Capthesin B (IOD/Area)	P
性别			
男	33	0.033(0.019, 0.074)	>0.05
女	17	0.056(0.025, 0.088)	
年龄(岁)			
<40	21	0.026(0.009, 0.070)	>0.05
$\geq 40$	29	0.041(0.029, 0.080)	
TNM 分期			
I、II	11	0.009(0.007, 0.080)	<0.05
III、IV	39	0.041(0.028, 0.078)	
分化程度			
中低分化	46	0.040(0.025, 0.081)	<0.05
高分化	4	0.008(0.006, 0.020)	
颈淋巴结转移			
是( $\bar{x} \pm s$ )	7	1.102 $\pm$ 0.044	<0.01
否	43	0.033(0.018, 0.063)	

### 2.2 鼻咽癌患者血清 Capthesin B 检测

ELISA 检测 106 例鼻咽癌患者治疗前后及健康体检者血清 Capthesin B 浓度。结果显示,鼻咽癌患者治疗前血清 Capthesin B 浓度明显高于健康体检组( $P < 0.05$ ),治疗 1.00(0.70, 3.00)个月的血清 Capthesin B 浓度显著降低( $P < 0.001$ ),治疗后鼻咽癌患者组和健康体检组之间无显著差异( $P > 0.05$ ),见表 2、图 2。

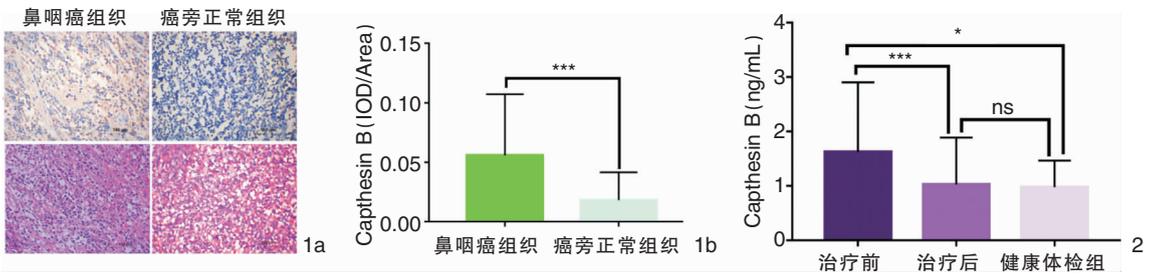
表 2 健康体检组与鼻咽癌患者治疗前后血清 Capthesin B 对比分析 [ ng/mL,  $Q_2(Q_1, Q_3)$  ]

分组	例数	Capthesin B	P
鼻咽癌组	106		
治疗前		1.23(0.64, 2.27)	<0.05*
治疗后		0.69(0.39, 1.42)	
健康组( $\bar{x} \pm s$ )	40	0.98 $\pm$ 0.49	>0.05**

注: \*  $P$  为健康组与鼻咽癌患者治疗前比较; \*\*  $P$  为健康组与鼻咽癌患者治疗后比较。

### 2.3 鼻咽癌患者血清中 Capthesin B 与鼻咽癌患者临床特征的关系

表 3 总结了鼻咽癌患者的临床病理特征,包括年龄、性别、EBVCA-IgG、EBVEA-IgA 和 TNM 分期<sup>[20]</sup>,结果表明血清 Capthesin B 浓度与年龄、性别无显著相关性( $P > 0.05$ )。TNM 分期 III、IV 期及有颈淋巴结转移、中低分化鼻咽癌患者血清 Capthesin B 浓度显著高于 I、II 期、无颈淋巴结转移、高分化者( $P < 0.05$ )。EBVCA-IgG、EBVEA-IgA 阳性患者的血清 Capthesin B 浓度显著低于阴性者( $P < 0.05$ )。



**图1** 鼻咽癌组织 Capthesin B 表达检测 1a:IHC 检测鼻咽癌组织及癌旁正常组织 Capthesin B 表达 (IHC ×400); 1b:鼻咽癌组织及癌旁正常组织 Capthesin B 表达定量分析(\*\*\*  $P < 0.001$ ) **图2** ELISA 实验检测鼻咽癌患者治疗前后及健康体检组血清 Capthesin B 浓度柱状图(\*  $P < 0.05$ ; \*\*\*  $P < 0.001$ ; <sup>ns</sup>  $P > 0.05$ )

**表3** 鼻咽癌患者血清 Capthesin B 浓度与临床指标的相关性分析 [ng/mL,  $Q_2(Q_1, Q_3)$ ]

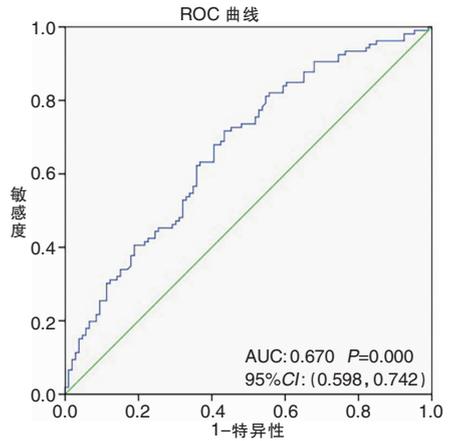
临床指标	例数	Capthesin B	P
性别			
男	83	1.19(0.60, 2.27)	>0.05
女	23	1.70(0.66, 2.20)	
年龄(岁)			
<40	24	1.68(0.62, 2.20)	>0.05
≥40	82	1.20(0.64, 2.28)	
TNM 分期			
I、II	21	1.14(0.60, 2.12)	<0.05
III、IV( $\bar{x} \pm s$ )	85	2.09 ± 1.50	
颈淋巴结转移			
是( $\bar{x} \pm s$ )	16	2.63 ± 1.67	<0.01
否	90	1.10(0.59, 2.14)	
分化程度			
中低分化	104	1.24(0.68, 2.27)	
高分化( $\bar{x} \pm s$ )	2	0.40 ± 0.06	<0.05
EBVCA-IgG			
阳性	39	0.80(0.54, 1.43)	<0.05
阴性	67	1.58(0.93, 2.29)	
EBVEA-IgA			
阳性	36	0.60(0.46, 1.19)	<0.001
阴性	70	1.71(1.03, 2.72)	

### 2.4 血清预测

基于鼻咽癌患者治疗前后血清 Capthesin B 水平,ROC 曲线下面积(AUC)为 0.670 ( $P < 0.001$ ),血清 Capthesin B 浓度临界值为 0.437 ng/mL,敏感性为 90.6%,特异性为 32.1%,提示血清 Capthesin B 可作为鼻咽癌患者治疗预后的参考指标,见图3。

### 3 讨论

尽管鼻咽癌治疗效果有了极大的改善,5 年生存率甚至 10 年生存率有了显著提高,但临床上大部分鼻咽癌初诊患者发现时已处晚期,伴多处转移,治疗效果往往不佳。故本研究试图寻找敏感、特异的生物标志物进行鼻咽癌转移预测及疗效评估。



**图3** ROC 曲线分析

Capthesin B 在多种人类癌症中高表达,是癌细胞分泌的一个重要物质<sup>[21-22]</sup>,血清 Capthesin B 浓度的变化不仅可用于预测肿瘤进展和预后,还可用于评价治疗效果。Capthesin B 作为一种新型血清蛋白生物标志物,在多种恶性肿瘤中被证实其与肿瘤侵袭转移有关<sup>[23-25]</sup>。同上述研究相同,本研究发现鼻咽癌颈淋巴结转移组 Capthesin B 水平明显高于无转移组,这充分提示 Capthesin B 与鼻咽癌转移密切相关,Capthesin B 可望成为鼻咽癌转移的预测指标。本研究中鼻咽癌患者原发组织中高表达的 Capthesin B 提示 Capthesin B 与鼻咽癌发生发展密切相关。前期研究表明 Capthesin B 可通过启动细胞保护性自噬发挥抗癌作用<sup>[26-27]</sup>。本实验结果显示 EBVCA-IgG、EBVEA-IgA 阳性患者的血清 Capthesin B 浓度更低,EBVCA-IgG、EBVEA-IgA 阴性患者的血清 Capthesin B 浓度更高,可能与 Capthesin B 启动细胞保护性自噬,进而抑制 EBV 病毒活动有关<sup>[26]</sup>。研究表明,血清高浓度 Capthesin B 可显著降低癌症患者 5 年生存率,目前越来越多的研究表明血清标志物浓度的变化可有效反映疾病活动性,进而评估疗效<sup>[23]</sup>。本研究检测了鼻咽癌患者治疗前和治疗后的血清 Capthesin B 浓度,结果表明,鼻

咽癌患者血清 Capthesin B 浓度与健康体检组相比有所升高,而治疗后患者血清 Capthesin B 浓度显著下降,临床分析表明,血清 Capthesin B 浓度与鼻咽癌 TNM 分期及分化程度密切相关,提示有血清 Capthesin B 浓度可作为鼻咽癌治疗预后的参考指标。综上所述,鼻咽癌患者 Capthesin B 高表达,有效治疗后患者血清 Capthesin B 显著降低,鼻咽癌颈淋巴结转移患者 Capthesin B 高于无转移组,提示 Capthesin B 参与鼻咽癌发生发展,可作为鼻咽癌治疗预后的参考指标。

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