

[DOI] 10.12016/j.issn.2096-1456.202440159

· 基础研究 ·

TROP2蛋白在涎腺腺样囊性癌中的表达及与患者预后的关系

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【摘要】 目的 探讨滋养层细胞表面抗原2(trophoblast cell-surface antigens 2, TROP2)在涎腺腺样囊性癌(salivary adenoid cystic carcinoma, SACC)中的表达,并分析其与临床病理特征之间的关系,明确TROP2的表达与涎腺腺样囊性癌患者预后的相关性。方法 获得单位伦理委员会的批准,采用免疫组织化学方法检测TROP2在85例SACC组织及各自癌旁组织中的表达情况,分析其表达情况与临床病理特征的关系;利用Kaplan-Meier法对40例SACC患者进行TROP2蛋白表达与患者术后五年无病生存期(disease-free survival, DFS)的关系进行分析;同时,采用Logistic回归模型分析影响涎腺腺样囊性癌患者预后的因素。结果 TROP2在SACC组织中的低表达或不表达率显著高于癌旁组织($P < 0.001$);TROP2低表达或不表达与SACC患者肿瘤的生长以及临床分期呈显著正相关性($P < 0.05$);Kaplan-Meier生存分析显示:TROP2蛋白低表达或不表达的SACC患者的DFS显著低于高表达患者($P < 0.05$),预后不良。Logistic回归模型预后分析显示:TROP2蛋白低表达或不表达($OR = 6.33$; $95\%CI: 1.37 \sim 29.20$; $P = 0.018$)与III-IV临床分期($OR = 5.37$; $95\%CI: 1.03 \sim 28.08$; $P = 0.046$)均为影响SACC患者预后的危险因素。结论 TROP2蛋白在SACC组织中低表达或不表达,患者预后不良,与肿瘤的生长、临床分期呈正相关,且TROP2低表达或不表达可作为SACC患者的独立预后不良的危险因素,TROP2为SACC患者预后不良的标志物。

【关键词】 涎腺腺样囊性癌; 预后; 免疫组织化学; TROP2; 生物标志物; T分期; 临床分期; 临床病理特征; 无病生存期; 生存分析

【中图分类号】 R78 **【文献标志码】** A **【文章编号】** 2096-1456(2024)10-0746-07

【引用著录格式】 董博,姚曼曼,尚宏悦,等. TROP2蛋白在涎腺腺样囊性癌中的表达及与患者预后的关[J]. 口腔疾病防治, 2024, 32(10): 746- . doi:10.12016/j.issn.2096-1456.202440159.

Expression of TROP2 protein in salivary adenoid cystic carcinoma and its correlation with the prognosis of patients with salivary adenoid cystic carcinoma DONG Bo, YAO Manman, SHANG Hongyue, YANG Kaicheng, LIU Tiejun. Department of Stomatology, the Fourth Hospital of Hebei Medical University, Shijiazhuang 050011, China
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【Abstract】 Objective To investigate the expression of trophoblast cell-surface antigen 2 (TROP2) in salivary adenoid cystic carcinoma (SACC) in order to analyze its relationship with TROP2 expression and clinicopathological features, as well as to clarify the correlation between TROP2 expression and the prognosis of patients with SACC. **Methods** with approval from the ethics committee, the expression of TROP2 in 85 SACC and paracancer tissue samples was detected by using the immunohistochemical method, and the relationship between TROP2 expression and clinicopathological characteristics was analyzed. The Kaplan-Meier method was used to analyze the relationship between TROP2 protein expression and 5-year disease-free survival (DFS) in 40 patients with SACC. Furthermore, the logistic regression model was used to analyze the prognostic factors of patients with SACC. **Results** The low or no expression rate of TROP2 in SACC tissues was significantly higher than that in paracancer tissues ($P < 0.001$). Low or no expres-

【收稿日期】 2024-04-19; **【修回日期】** 2024-06-12

【基金项目】 河北省自然科学基金(H2022206410);河北省科技部重点研发计划项目(22377779D)

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sion of TROP2 was significantly positively correlated with tumor growth and clinical staging in patients with SACC ($P < 0.05$). Kaplan-Meier survival analysis showed that the DFS of patients with SACC with low or no expression of TROP2 protein was significantly lower than those of patients with high expression of TROP2 protein ($P < 0.05$), and the prognosis was poor. The logistic regression model showed that low or no expression of TROP2 protein ($OR = 6.33$; 95%CI: 1.37-29.20; $P = 0.018$) and III-IV clinical staging ($OR = 5.37$; 95% CI: 1.03-28.08; $P = 0.046$) were risk factors affecting the prognosis of patients with SACC. **Conclusion** Low or no expression of TROP2 protein in SACC tissues leads to poor prognosis of patients and is positively correlated with tumor growth and clinical staging. In addition, low or no expression of TROP2 can be used as an independent prognostic risk factor for poor prognosis in patients with SACC, and TROP2 is a marker of poor prognosis in patients with SACC.

【Key words】 salivary gland adenoid cystic carcinoma; prognosis; immunohistochemistry; TROP2; biomarker; T stage; clinical stage; clinicopathological features; disease-free survival; survival analysis

J Prev Treat Stomatol Dis, 2024, 32(10): 00-00.

【Competing interests】 The authors declare no competing interests.

This study was supported by the grants from Natural Science Foundation of Hebei Province (No. H2022206410); the Key Research and Development Plan Project of the Science and Technology Department Of Hebei Province (No. 2237779D).

涎腺腺样囊性癌(salivary adenoid cystic carcinoma, SACC)是一种相对罕见的恶性肿瘤^[1],好发于上腭部小唾液腺及腮腺,其生长缓慢,有很强的侵袭性,很难做到彻底根治性切除^[2]。当前常规治疗方式仍然是手术联合或不联合放射治疗,患者5年总生存率68.0%^[3]。神经周浸润是SACC的局部进展特征,这一特征在肿瘤的复发和转移中起重要作用,高复发率和转移率是治疗SACC的难点^[4-5]。由于唾液腺癌的高异质性,致使很少有充分的临床试验可用于确定其最佳的全身治疗方法^[6]。深入研究SACC的生物标志物,有利于SACC早期诊治及对预后判断。最近研究发现,人滋养层细胞表面抗原2(trophoblast cell-surface antigens 2, TROP2)在唾液腺癌中存在阳性表达情况,提示TROP2可能作为唾液腺癌的潜在治疗靶点^[7]。TROP2是一种I型跨膜类糖蛋白,被肿瘤相关钙信号转导子2(tumor associated calcium signal transducer 2, TACSTD2/TROP2)基因编码^[8-9]。目前TROP2在肿瘤细胞中的表达与功能呈两极分化现象,例如在肺腺癌细胞系中观察到TROP2的低表达,其促进肿瘤的增殖与迁移能力^[10]。然而在多数头颈部恶性肿瘤中,均观察到了TROP2的高表达现象,例如鼻咽癌、喉鳞状细胞癌、甲状腺癌、口腔鳞状细胞癌等,并且TROP2过表达可刺激肿瘤细胞增殖和生长^[11-14]。尽管目前在多种实体瘤中做了TROP2相关研究,但在涎腺肿瘤中关于TROP2的研究较少,尤其是SACC, TROP2在SACC中的具体生物学功能和预后关系还有待研究。本文旨在明

确TROP2在SACC组织表达水平,并分析其与各项临床病理因素之间的相关性以及与SACC预后的关系。

1 材料和方法

1.1 材料

1.1.1 病例及样本来源 该研究回顾性分析了2013年至2023年在河北医科大学第四医院口腔颌面外科诊断为涎腺腺样囊性癌并接受治疗的患者共85例,其中发生于腭部31例,其他部位10例(颈前2、牙龈2、上唇3、颊部2、上颌骨1),口底16例,腮腺12例,舌下腺4例,舌部5例,颌下腺7例。并收集经福尔马林固定石蜡包埋的组织块,包括肿瘤组织和癌旁组织(距肿瘤空间距离为2 cm)。本研究采取自身对照方法,因此选取的标本包括包括85例SACC组织和各自的癌旁组织,所有的受试者在活检之前均未接受手术治疗以及放化疗。

1.1.2 主要试剂 TROP2兔抗人单克隆抗体(SP295, Abcam, 英国, 稀释比为1:2 500),酶标羊抗鼠/兔IgG聚合物(PV-6000D, 中杉金桥, 中国)。

1.2 方法

1.2.1 病例资料 于河北医科大学第四医院病案室收集患者完整的临床病理信息,包括年龄、性别、肿瘤部位、肿瘤大小、淋巴结转移、远处转移、临床分期、血管浸润和神经周浸润、吸烟史、饮酒史。组织学分类根据第五版WHO(2022)涎腺肿瘤进行分类^[15],并根据第八版AJCC癌症分期手册进行分期^[16]。定义无病生存期(disease-free survival,

DFS)为从第一次手术治疗结束后癌症出现复发或转移或因任何原因死亡的时间。采用门诊复查和电话随访,随访截止日期定为2023年12月31日,以5年随访时间为标准,最终从85例样本中得到符合标准的40例样本做DFS预后分析。本研究方案获得河北医科大学第四医院伦理委员会批准(审批号:2022K7211),所有参与者知情同意。

1.2.2 免疫组化 采用免疫组织化学EliVision两步法检测SACC组织及癌旁组织中TROP2的表达情况。SACC组织蜡块常规切片,干燥、脱蜡并水化,30%过氧化氢灭活内源性过氧化物酶,EDTA高压修复抗原,多次洗涤后,滴加一抗TROP2兔单克隆抗体室温下孵育3h,反复洗涤后,滴加二抗酶标羊抗鼠/兔IgG聚合物孵育30min,常规DAB显色,苏木精复染,酒精脱水吹干,中性树胶封片。用缓冲液代替一抗作阴性对照,用已知阳性切片作阳性对照。

免疫组化结果的解释和评估:利用半定量H评分法^[17-19](H-Score)对TROP2表达进行评分,由两名经验丰富的病理医师单盲法使用光学显微镜对每个切片随机选择3个视野,进行细胞膜表达评估,采取以下染色强度评分:0表示无染色;1+表示弱染色;2+表示中度染色;3+表示强染色。将每个强度水平的细胞总数所占整体区域的百分比乘以相应的强度分数,得出强度百分比分数,最后通过将四个强度百分比分数相加得出最终染色分数;最终的H评分范围在0~300分,最终最低染色评分为0(无染色),最高的评分为300(100%的细胞呈3+染色强度),TROP2无表达H-Score为0,低表达H-Score为1~100,中度表达H-Score为101~200,高表达H-Score为201~300。后续分析中对所有患者依照中位H-Score进行分组,分为相对低表达或不表达组(low or no expression)(H-Score ≤ 70)和相对高表达组(high expression)(H-Score > 70)。

1.3 统计学分析

使用GraphPad Prism 10.1软件进行统计分析,使用配对t检验分析两组之间的差异性。数据整理与统计分析基于风暴统计平台(www.medsta.cn/software)和R version 4.3.0(2023-04-21)完成,统计具备5年随访时间条件的患者的复发和转移数据,剔除失访人群,使用Kaplan-Meier方法计算患者无病生存期(DFS)的生存曲线并使用对数秩检验进行分析;使用卡方检验分析TROP2与所有患者临床病理参数之间的关系;利用单变量及多变量

Logistic回归模型拟合DFS作为结果,且在使用单变量分析中将 $P < 0.05$ 的变量进行多变量Logistic比例回归分析预后风险因素。 $P < 0.05$ 为差异具有统计学意义。

2 结果

2.1 TROP-2在涎腺腺样囊性癌组织和癌旁组织中的表达情况

TROP2在85例SACC组织和癌旁组织的蛋白表达见表1。TROP2在SACC组织和癌旁组织中的表达强度具有差异性,在SACC组织中TROP2低表达的标本最多,占54.12%(46/85),高表达标本最少,占7.06%(6/85);而在癌旁组织中高表达的标本最多,占50.59%(43/85),不表达标本最少,占5.88%(5/85)($P < 0.001$)。SACC组织中TROP2中位H-score为70,癌旁组织中位H-score为225,与癌旁组织相比,SACC组织中TROP2表达水平显著降低, ($P < 0.0001$,图1),使用免疫组织化学(IHC)方法对SACC中的TROP2蛋白进行染色,镜下放大200倍和400倍,发现TROP2蛋白均表达于胞膜(图2)。

2.2 TROP2表达与涎腺腺样囊性癌临床病理特征之间的关系

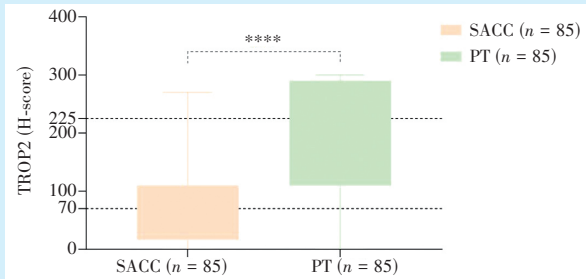
85例SACC患者的中位年龄为59岁(26~88岁),其中43.53%的患者为男性,56.47%的患者为女性。大多数肿瘤位于上腭(36.47%),所有患者术前均未放化疗,术中均接受了原发肿瘤切除。依照TROP2的中位H-Score为70,将所有患者分为低表达或不表达组($n = 46$)和高表达组($n = 39$),由于部分患者的蜡块无法准确分辨肿瘤组织的分化程度,故本统计中并未纳入TROP2蛋白表达与组织分化之间的关系。

分析TROP2表达情况与SACC临床病理特征

表1 TROP2在SACC组织和癌旁组织中的表达

TROP2 expression	Total (n, %)	Tissue type (n, %)		χ^2	P
		PT	SACC		
No	19 (11.18)	5 (5.88)	14 (16.47)	46.82	< 0.001
Low	62 (36.47)	16 (18.82)	46 (54.12)		
Moderate	40 (23.53)	21 (24.71)	19 (22.35)		
High	49 (28.82)	43 (50.59)	6 (7.06)		

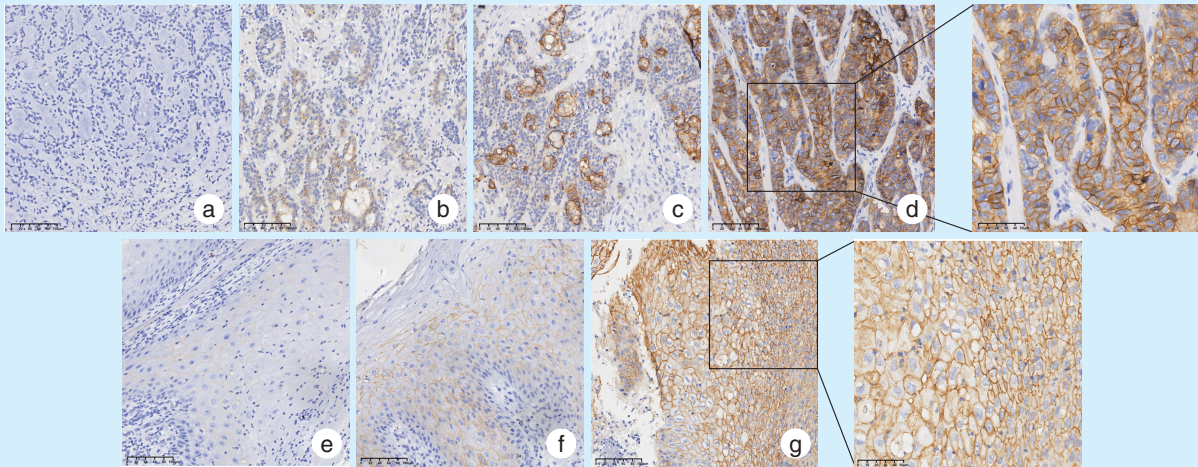
TROP2: trophoblast cell-surface antigens 2. SACC: salivary adenoid cystic carcinoma. PT: paracancer tissues



The TROP2 H-score of PT was significantly higher than that of SACC ($P < 0.0001$). TROP2: trophoblast cell-surface antigens 2. SACC: salivary adenoid cystic carcinoma tissue. PT: paracancer tissue

Figure 1 Box plot of TROP2 protein expression H score of SACC and paracancer tissue samples

图1 SACC组织和癌旁组织中TROP2蛋白表达H评分的箱线图



a: no expression of TROP2 in SACC (staining intensity score 0, $\times 200$). b: low expression of TROP2 in SACC (staining intensity score 1+, $\times 200$). c: the moderate expression of TROP2 in SACC (staining intensity score 2+, $\times 200$). d: high expression of TROP2 in SACC (staining intensity score 3+, $\times 200$, $\times 400$). e: low expression of TROP2 in paracancer tissue (staining intensity score 1+, $\times 200$). f: moderate expression of TROP2 in paracancer tissue (staining intensity score 2+, $\times 200$). g: high expression of TROP2 in paracancer tissue (staining intensity score 3+, $\times 200$, and $\times 400$). TROP2: trophoblast cell-surface antigens 2. SACC: salivary adenoid cystic carcinoma tissue

Figure 2 TROP2 protein was expressed in the cell membranes of SACC and paracancer tissues

图2 SACC组织和癌旁组织中TROP2蛋白均表达于胞膜

的关系,将TROP2表达与年龄、性别、分期、淋巴结转移、神经周浸润、血管侵犯、吸烟史以及饮酒史等进行比较,结果显示TROP2低或不表达与肿瘤大小增加和III-IV临床分期之间存在明显的正相关性(表2)。

2.3 TROP2表达与SACC 5年无病生存期(DFS)之间的关系

85例患者,以5年随访时间为标准,8例失联,37例未满5年随访时间,得到当前SACC队列($n = 40$)的无病生存率为45.0%,中位无病生存时间为67.0个月(范围为1~97个月),TROP2低表达或不表达患者5年无病生存率为32.1%,高表达患者5年无病生存率为75.0%,10名患者(45.4%)死亡,15名患者(68.2%)出现疾病复发或转移(图3)。

单因素 Logistic 回归分析结果显示,TROP2低

表达或不表达($OR = 6.33$; $95\%CI: 1.37 \sim 29.20$; $P = 0.018$)的患者DFS较短,多因素 Logistic 回归分析结果显示,TROP2低表达或不表达对患者差的DFS有重要影响($OR = 5.37$; $95\%CI: 1.03 \sim 28.08$; $P = 0.046$)(表3)。

3 讨论

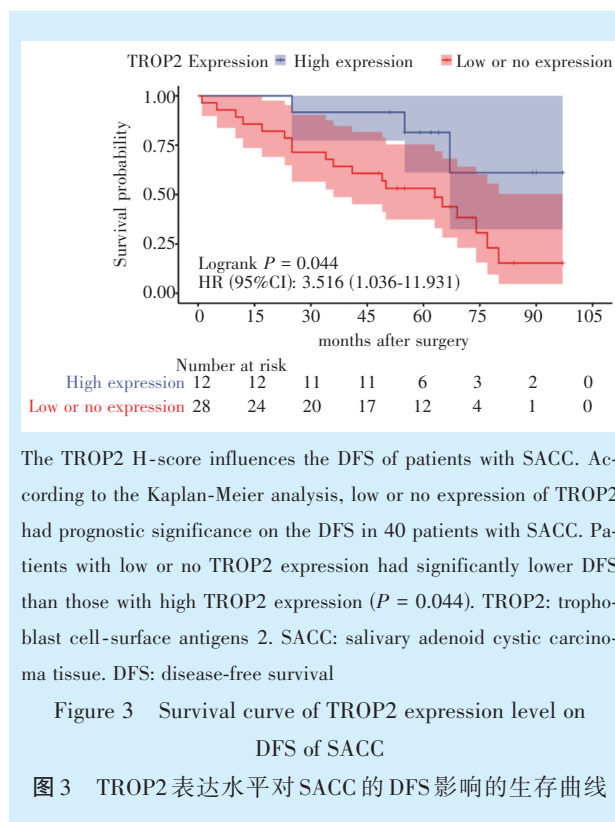
在以往的研究中发现,TROP2在各种癌组织中高表达,在正常组织中低表达或不表达,例如在乳腺癌、卵巢癌、胰腺癌、胃癌、结肠癌、前列腺癌^[20-25]等均出现TROP2高表达趋势。TROP2在癌组织中高表达并能促进肿瘤的增殖、复发和迁移似乎已成为一种相当成熟的结论^[26]。本研究对更罕见的涎腺腺样囊性癌的资料进行了汇总和分析,发现TROP2在SACC组织中呈现低表达或不表

表2 TROP2表达情况与SACC临床病理特征的关系

Table 2 Relationship between TROP2 expression and clinicopathological features of SACC TROP2 expression(n,%)

Characteristics	Total patients (n, %)	TROP2 expression (n, %)		χ^2	P
		Low or no (n, %)	High (n, %)		
Age				0.011	0.906
>59	42 (49.41)	23 (50.00)	19 (48.72)		
≤59	43 (50.59)	23 (50.00)	20 (51.28)		
Sex				0.18	0.668
Female	48 (56.47)	25 (54.35)	23 (58.97)		
male	37 (43.53)	21 (45.65)	16 (41.03)		
Localization				4.161	0.655
Palatine	31 (36.47)	17 (36.96)	14 (35.90)		
Other	10 (11.76)	7 (15.22)	3 (7.69)		
Floor of mouth	16 (18.82)	8 (17.39)	8 (20.51)		
Parotid gland	12 (14.12)	4 (8.70)	8 (20.51)		
Sublingual gland	4 (4.71)	2 (4.35)	2 (5.13)		
Tongue	5 (5.88)	3 (6.52)	2 (5.13)		
Salivary gland	7 (8.24)	5 (10.87)	2 (5.13)		
Tumor size				8.56	0.036
T1	17 (20.00)	6 (13.04)	11 (28.21)		
T2	32 (37.65)	14 (30.43)	18 (46.15)		
T3	25 (29.41)	18 (39.13)	7 (17.95)		
T4	11 (12.94)	8 (17.39)	3 (7.69)		
Lymph node metastases				3.666	0.160
N0	74 (87.06)	42 (91.30)	32 (82.05)		
N1	6 (7.06)	1 (2.17)	5 (12.82)		
N2	5 (5.88)	3 (6.52)	2 (5.13)		
Distant metastases				0.491	0.482
M0	60 (70.59)	31 (67.39)	29 (74.36)		
M1	25 (29.41)	15 (32.61)	10 (25.64)		
metastases				0.22	0.64
No	50 (58.82)	17 (36.96)	14 (35.90)		
Yes	35 (41.18)	7 (15.22)	3 (7.69)		
Stage (AJCC)				4.973	0.026
I+II	39 (45.88)	16 (34.78)	23 (58.97)		
III+IV	46 (54.12)	30 (65.22)	16 (41.03)		
Perineural infiltration				2.172	0.141
No	55 (64.71)	33 (71.74)	22 (56.41)		
Yes	30 (35.29)	13 (28.26)	17 (43.59)		
Vascular invasion				0.021	0.884
No	82 (96.47)	45 (97.83)	37 (94.87)		
Yes	3 (3.53)	1 (2.17)	2 (5.13)		
Smoke				0.022	0.883
No	66 (77.65)	36 (78.26)	30 (76.92)		
Yes	19 (22.35)	10 (21.74)	9 (23.08)		
Wine				0.156	0.693
No	67 (78.82)	37 (80.43)	30 (76.92)		
Yes	18 (21.18)	9 (19.57)	9 (23.08)		

TROP2: trophoblast cell-surface antigens 2. SACC: salivary adenoid cystic carcinoma tissue



The TROP2 H-score influences the DFS of patients with SACC. According to the Kaplan-Meier analysis, low or no expression of TROP2 had prognostic significance on the DFS in 40 patients with SACC. Patients with low or no TROP2 expression had significantly lower DFS than those with high TROP2 expression ($P = 0.044$). TROP2: trophoblast cell-surface antigens 2. SACC: salivary adenoid cystic carcinoma tissue. DFS: disease-free survival

Figure 3 Survival curve of TROP2 expression level on DFS of SACC

图3 TROP2表达水平对SACC的DFS影响的生存曲线

达倾向,而在癌旁组织中则呈高表达,且TROP2低表达或不表达对患者较差的预后起着重要的影响,得出的结果与之前的研究结论相反,表明深入研究TROP2在SACC中异常表达有其必要性。

TROP2表达丧失的情况可归因于多种因素,表观遗传因素被确定为癌症中TROP2表达的重要调节剂^[27]。Sin等^[28]报道对肝癌中的TROP2进行免疫组化检测,几乎检测不到其表达,对肝癌的DNA样本启动高甲基化出现TROP2的下调,且TROP2的缺失与患者总体生存率低有明显相关性,证明TROP2可能通过DNA甲基化在表观遗传上失活;同时TROP2表达受各种癌细胞中TACSTD2基因启动子甲基化的调节^[29],Lin等^[10]在肺腺癌组织中观察到TROP2的低表达和不表达现象,同时证明了TROP2缺失除了与DNA甲基化有关,还可能与TROP2上游启动子区域的杂合性缺失(loss of heterozygosity, LOH)密不可分。除此之外,Lin等^[10]还发现TROP2 mRNA在一些癌症组织(如乳腺癌、肾癌、肺癌、前列腺癌和胎盘癌)中的表达下调,TROP2在多种肿瘤中的表达水平与肿瘤的进展密切相关。尽管有些SACC组织的H-score=0,但其癌旁组织中TROP2却有表达现象,提示了TROP2可能参与了肿瘤的发生和发展过程,癌组织中TROP2不表达可能与上述DNA甲基化和LOH

表3 单因素和多因素 Logistic 回归分析影响 SACC 患者 DFS 的危险因素

Table 3 Logistic univariate and multivariate analyses of risk factors affecting the DFS in patients with SACC

Factors	Univariate analysis		Multivariate analysis	
	P	OR (95%CI)	P	OR (95%CI)
TROP2 expression				
High				
Low or no	0.018	6.33 (1.37 - 29.20)	0.046	5.37 (1.03 - 28.08)
Age				
≤59				
>59	0.387	1.75 (0.48 - 2.56)		
Sex				
female				
male	0.676	1.31 (0.37 - 4.64)		
Tumor size				
T1				
T2	0.497	0.50 (0.07 - 3.70)		
T3	0.208	3.50 (0.50 - 24.56)		
T4	0.437	0.33 (0.02 - 5.33)		
Stage (AJCC 8 th ed)				
I+II				
III+IV	0.008	7.92 (1.71 - 36.63)	0.019	6.89 (1.37 - 34.77)
Perineural invasion				
No				
Yes	0.678	0.75 (0.19 - 2.91)		
Vascular invasion				
No				
Yes	0.998	0.00 (0.00 - Inf)		
Smoke				
No				
Yes	0.972	0.98 (0.24 - 3.93)		
Lymph node metastases				
N0				
N1	0.41	0.35 (0.03 - 4.25)		
N2	0.41	0.35 (0.03 - 4.25)		
Tipple				
No				
Yes	0.97	1.03 (0.23 - 4.58)		

CI: confidence interval; OR: odds ratio; DFS: disease-free survival; AJCC: American Joint Committee on Cancer. TROP2: trophoblast cell-surface antigens 2. SACC: salivary adenoid cystic carcinoma tissue

有关,也可能与基因突变或染色体缺失等遗传变异相关,具体原因需要后续相关实验验证。

本研究发现了 TROP2 在肿瘤细胞中的表达,且主要定位于细胞膜。免疫组化检测结果显示,与癌旁组织相比,TROP2 在肿瘤细胞中的表达明显降低,甚至无表达,在患者 5 年无病生存率的 KaplanMeier 分析中,可观察到 TROP2 低表达与患者较差的 DFS 显著相关,且 Logistic 回归分析显示,TROP2 表达水平愈低,其预后越差,表明 TROP2 可

能是 SACC 患者预后的一个独立指标。这些结果与 Sin 等^[28]的研究结果一致,TROP2 在肝细胞癌 (hepatocellular carcinoma, HCC) 中出现低表达或不表达现象,并且使用 Kaplan-Meier 分析和对数秩和检验,发现 TROP2 的下调与 HCC 患者预后密切相关。

本研究的局限性在于 SACC 患者样本量较少,部分患者未能常规随访,无法得到患者最新的临床数据,可能对患者预后风险因素的评估造成一定的误差。

综上,本研究结果显示,TROP2 在 SACC 中低表达或不表达,在癌旁组织中高表达,且 TROP2 低表达或不表达可预测患者较差的 DFS,但其中的机制尚不清楚,值得进一步研究。

【Author contributions】 Dong B analyzed the data and wrote the article. Yao MM collected, processed and modified the data. Shang HY sorted out the data and revised the article. Yang KC analyzed the data and revised the article. Liu TJ designed the study and reviewed the article. All authors read and approved the final manuscript as submitted.

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