# 乳腺癌患者血清可溶性T细胞免疫球蛋白黏蛋白分子-3与其配体的表达及临床意义

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**摘　要**:[目的]评价乳腺癌患者血清可溶性T细胞免疫球蛋白及黏蛋白分子-3 (souble T cell immunoglobulin and mucin-domain containing molecule-3,sTim-3)及其配体半乳糖凝集素-9(galactose lectin-9,Galectin-9)、癌胚抗原相关细胞黏附分子1 (carcino-embryonic antigen related cellular adhesion molecule-1,CEACAM-1)表达水平,并探讨其临床意义。[方法]收集2019年7月至2020年10月武汉市中西医结合医院甲乳外科住院的乳腺癌患者90例血清,同期选择选择60名年龄相应匹配的健康体检者血清为对照组。酶联免疫吸附法检测乳腺癌患者和对照组血清sTim-3、Galectin-9、CEACAM-1表达水平。ROC曲线分析血清sTim-3、Galectin-9对乳腺癌的诊断学效能。[结果]乳腺癌患者血清sTim-3[2.59(1.78~4.03) ng/ml]和Galectin-9[2.20(1.55~3.05) ng/ml]表达水平显著性高于对照组sTim-3 [1.79(1.19~2.45) ng/ml]和Galectin-9 [1.59(1.18~2.15) ng/ml](*P*<0.05),乳腺癌患者血清CEACAM-1水平与对照组相比无显著性差异(*P*=0.622)。乳腺癌患者血清sTim-3表达水平与年龄、肿瘤大小、临床分期、腋窝淋巴结转移显著性相关(*P*<0.05),与组织学分级、Ki-67表达无显著性相关(*P*>0.05)。Galectin-9表达水平与临床病理学特征无显著性相关(*P*>0.05)。乳腺癌患者血清CEACAM-1表达水平随组织学分级的升高而增高(*P*=0.025),与其他临床病理学特征无显著性相关(*P*>0.05)。sTim-3和Galectin-9诊断乳腺癌的曲线下面积分别为0.741(95%CI:0.666~0.816),0.692(95%CI:0.599~0.785)。[结论]乳腺癌患者血清sTim-3及其配体Galectin-9表达水平显著性上调,血清sTim-3与多个临床病理学特征相关,对乳腺癌的诊断具有一定价值。CEACAM-1在乳腺癌患者血清中表达未见升高,但与组织学分级存在一定关联,其与乳腺癌的关系有待进一步研究。

**主题词**:乳腺癌;T细胞免疫球蛋白黏蛋白分子-3;半乳糖凝集素9;癌胚抗原相关细胞黏附分子1
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# Expression of Serum Soluble T Cell Immunoglobulin Mucin Molecule-3 and Its Ligand in Breast Cancer Patients and Clinical Significance

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**Abstract**: [Objective] To analyze the expression levels of soluble T cell immunoglobulin and mucin molecule-3(sTim-3) and its ligand galactose lectin-9(Galectin-9) and carcinoembryonic antigen-associated cell adhesion molecule-1 (CEACAM-1) in serum of patients with breast cancer, and to explore their clinical significance. [Methods] The 90 patients with breast cancer were collected from the Department of Thyroid-Breast Surgery, Wuhan Traditional Chinese and Western Medicine Hospital from July 2019 to October 2020. At the same time, the 60 healthy subjects with corresponding age matching were selected as the control group. The expression levels of sTim-3, Galectin-9 and CEACAM-1 in serum of breast cancer patients and control group were detected by enzyme-linked immunosorbent assay (Elisa). The diagnostic efficacy of serum sTim-3 and Galectin-9 on breast cancer was analyzed by ROC curve. [Results] The expression levels of serum sTim-3[2.59 (1.78~4.03) ng/ml] and Galectin-9 [2.20 (1.55~3.05) ng/ml] in breast cancer patients were significantly higher than those in normal control groups[1.79(1.19~2.45) ng/ml] and [1.59(1.18~2.15) ng/ml](*P*<0.05). There was no significant difference in serum CEACAM-1 between breast cancer patients and normal control group. The level of serum sTim-3 expression in breast cancer patients was significantly correlated with age, tumor size, clinical stage and axillary lymph node metastasis. The difference was statistically significant(*P*<0.05), but not correlated with histological grade and Ki-67 expression(*P*>0.05). There was no significant correlation between the expression of Galectin-9 and clinicopathological data. The level of serum CEACAM-1 expression in patients with breast cancer increased with the increase of histological grade, and the difference was statistically significant(*P*<0.05). There was no significant correlation with other clinicopathological data(*P*>0.05). The area under the curve and 95%CI of sTim-3 and Galectin-9 in the diagnosis of breast cancer were 0.741(95%

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CI: 0.666~0.816) and 0.692 (95%CI: 0.599~0.785), respectively.[Conclusion] The expression level of serum sTim-3 and its ligand Galectin-9 in breast cancer patients were significantly higher. Serum sTim-3 is related to clinicopathological data, which has a certain value in the diagnosis of breast cancer. The expression of CEACAM-1 in the serum of breast cancer patients is not increased, but there is a certain correlation with histological grade. The relationship between CEACAM-1 and breast cancer needs to be further studied.
**Subject words**: breast cancer; T cell immunoglobulin mucin domain molecule 3; galactin-9; carcinoembryonic antigen associated cell adhesion molecule 1

近年来，针对肿瘤免疫逃逸机制开展的肿瘤免疫疗法取得了令人瞩目的临床效果，负性免疫检查点的发现将肿瘤免疫治疗研究推向高潮[1]。负性免疫检查点分子 Tim-3 是 Tims 家族成员，研究发现 Tim-3 与程序性死亡受体 1 (programmed cell death protein 1,PD-1) 联合阻断增强了抗肿瘤免疫力并抑制了肿瘤生长,可作为肿瘤免疫治疗靶点[2-3]。在恶性实体瘤肿瘤组织和细胞内 Tim-3 高表达并与肿瘤的发生发展预后相关。Tim-3 作为负性免疫检查点分子能增强免疫耐受,抑制抗肿瘤免疫[4]。Tim-3 以可溶性 T 细胞免疫球蛋白及黏蛋白分子-3(souble T cell immunoglobulin and mucin-domain containing molecule-3,sTim-3)存在,缺少黏蛋白和跨膜区,在肝细胞癌中的研究表明,Tim-3 参与肿瘤的进展,sTim-3 可作为肝细胞癌预后血清学标志物[5]。Tim-3 具有独特的 IGV 结构域,使其能与相应的配体,如半乳糖凝集素-9(galactose lectin-9,Galectin-9)、癌胚抗原相关细胞黏附分子 1(carcino-embryonic antigen related cellular adhesion molecule-1,CEACAM-1) 发生特异性结合,并诱导 T 细胞耗竭或无能,肿瘤微环境中削弱机体的抗肿瘤免疫应答，进而导致肿瘤免疫逃逸的发生[6]。目前国内外关于 Tim-3 及其配体 Galectin-9、CEACAM-1 研究多集中于组织和细胞中的表达,在乳腺癌患者血清中表达的研究较为少见。本研究通过酶联免疫吸附法检测 90 例乳腺癌患者及 60 名健康体检者血清 sTim-3、Galectin-9、CEACAM-1 表达水平，探讨其表达与乳腺癌患者临床病理特征的关系,有助于明确 Tim-3 及其配体 Galectin-9、CEACAM-1 在乳腺癌发生发展中的作用。

## 1 资料与方法

### 1.1 研究对象

收集 2019 年 7 月至 2020 年 10 月武汉市中西医结合医院甲乳外科住院的乳腺癌患者 90 例血清。纳入标准：①诊断符合 2018 年版乳腺癌诊疗规范；②纳入研究前未接受手术、放化疗或免疫靶向治疗；③自愿参与本研究；④临床病理资料齐全。排除标准:合并其他自身免疫性疾病,肿瘤,糖尿病或其他脏器损伤性疾病的患者。另同期选取 60 名年龄相匹配体检健康女性作为对照组。查阅临床病历,统计乳腺癌患者的临床病理学资料,包括年龄、肿瘤大小、组织学分级、TNM 分期、淋巴结转移、Ki-67 表达。本研究经武汉市中西医结合医院伦理委员会批准。

### 1.2 研究方法

#### 1.2.1 试剂与仪器

Tim-3(批号:DY2365)、Galectin-9(批号:DY2045)和 CEACAM-1(批号:DY2244)酶联免疫试剂盒均购自美国 R&D 公司。酶标仪为 Thermo Scientific Multiskango 全波长酶标仪。CEA、CA15-3 试剂盒来自北京源德生物有限公司。CEA、CA15-3 检测仪器为北京源德公司 YME JETLIA-962 发光仪。

#### 1.2.2 标本采集与实验方法

受试者空腹抽取 4 ml 静脉血于无添加剂的真空红色采血管中，待血液凝固后 3 500 r/min 离心 10 min 后分离血清,分装至无菌 EP 管并冻存至–80 ℃冰箱备用。酶联免疫吸附法检测血清 sTim-3、Galectin-9、CEACAM-1 表达水平，所有步骤严格按照试剂盒说明书操作。化学发光法检测 CEA、CA15-3 水平。

### 1.3 统计学处理

采用 SPSS16.0 统计软件分析数据,计量资料符合正态分布的以均值±标准差表示，非正态分布的以四分位间距表示。非正态分布数据的总体均值比较使用 Mann-Whitney *U* 检验（两组比较）或 Kruskal-Wallis *H* 检验（多组比较）。ROC 曲线分析 sTim-3、Galectin-9、CEA 和 CA15-3 对乳腺癌的诊断效能。*P*<0.05 为差异有统计学意义。

## 2 结 果

### 2.1 乳腺癌患者与健康对照组血清 sTim-3 及其配体水平比较

与健康对照组相比，乳腺癌患者血清 sTim-3、Galectin-9、CEA 和 CA15-3 表达水平呈显著性上升,差异有统计学意义(*P*<0.05)(Table 1)。

### 2.2 乳腺癌患者血清 sTim-3 及其配体 Galectin-9、CEACAM-1 表达与临床病理学特征的相关性

乳腺癌患者血清 sTim-3 表达水平在大于 50 岁的乳腺癌患者中的表达更高,并且在肿瘤大于 2 cm、临床分期较晚、发生腋窝淋巴结转移患者中的表达显著性升高(*P*<0.05),与组织学分级、Ki-67 表达均无相关性(*P*>0.05)。Galectin-9 表达水平与乳腺癌患者临床病理参数无显著性相关（*P*>0.05)。乳腺癌患者血清 CEACAM-1 表达水平随组织学分级的升高而增高,与其他病理学参数无显著性相关(*P*>0.05)(Table 2)。

### 2.3 ROC 曲线分析

ROC 曲线评估 sTim-3、Galectin-9、CEA 和 CA153 对乳腺癌诊断效能，sTim-3 曲线下面积 AUC=0.741, 95%CI: 0.666~0.816。sTim-3 以 2.83 ng/ml为临界值时，约登指数最大为 0.394,灵敏度为 46.67%，特异度为 92.75%。Galectin-9 的曲线下面积为 0.692 (95%CI:0.599~0.785)。Galectin-9 临界值为 2.01 ng/ml 时,约登指数最大为 0.334,此时灵敏度为 58.9%,特异度为 74.51%。CEA、CA15-3 曲线下面积分别为 AUC=0.595(95%CI:0.504~0.687)、AUC=0.651(95%CI:0.562~0.739)。当 CEA、CA153 以 0.81 μg/L、7.62 KU/L 为临界值时，灵敏度分别为 73.26%、76.54%，特异度分别为 44.62%、49.23%(Figure 1)。

**Table 1 Comparison of serum sTim-3 and its ligand expression levels between breast cancer patients and control group**

| Characteristic | Breast cancer(n=90) | Controls(*n*=60) | *Z* | *P* |
|---|---|---|---|---|
| sTim-3(ng/ml) | 2.59(1.78~4.03) | 1.79(1.19~2.45) | −5.202 | <0.001 |
| Galectin-9(ng/ml) | 2.20(1.55~3.05) | 1.59(1.18~2.15) | −3.633 | <0.001 |
| CEACAM-1(ng/ml) | 19.51(16.31~23.37) | 19.53(15.95~22.18) | −0.496 | 0.621 |
| CEA(μg/L) | 1.22(0.75~1.95) | 1.00(0.60~1.70) | −2.015 | 0.044 |
| CA15-3(KU/L) | 11.32(7.78~20.67) | 8.27(5.63~14.45) | −3.132 | 0.002 |

**Table 2 Association of serum sTim-3 and its ligand expression and characteristics in breast cancer patients(ng/ml)**

| Characteristic | N | sTim-3 | Galectin-9 | CEACAM-1 |
|---|---|---|---|---|
| Age(years old) | | | | |
| ≤50 | 25 | 1.82(1.56~2.45) | 1.91(1.12~2.82) | 17.75(15.43~27.34) |
| >50 | 65 | 3.11(2.27~4.56) | 2.35(1.74~3.09) | 19.60(16.39~22.05) |
| *Z* | | −3.257 | −1.880 | −0.179 |
| *P* | | 0.001 | 0.061 | 0.858 |
| Tumor size(cm) | | | | |
| ≤2 | 35 | 2.42(1.65~3.45) | 2.22(1.58~2.66) | 18.30(15.89~22.20) |
| >2 | 55 | 3.31(1.82~4.90) | 2.13(1.43~3.06) | 20.52(16.35~23.52) |
| *Z* | | −2.338 | −0.069 | −0.644 |
| *P* | | 0.019 | 0.949 | 0.520 |
| Grade | | | | |
| Ⅰ~Ⅱ | 67 | 2.72(1.89~4.05) | 2.25(1.43~3.06) | 18.51(15.82~21.97) |
| Ⅲ | 23 | 2.49(1.71~4.20) | 2.10(1.57~2.81) | 22.58(16.57~31.74) |
| *Z* | | −0.463 | −0.051 | −2.247 |
| *P* | | 0.646 | 0.964 | 0.025 |
| TNM stage | | | | |
| Ⅰ | 22 | 2.39(1.36~2.94) | 2.00(1.52~2.79) | 17.93(15.45~21.98) |
| Ⅱ | 45 | 2.52(1.81~4.16) | 2.23(1.37~3.01) | 19.60(16.37~22.08) |
| Ⅲ~Ⅳ | 23 | 3.77(2.22~5.95) | 2.35(1.72~4.29) | 21.84(15.70~28.89) |
| *Z* | | 9.455 | 0.949 | 1.604 |
| *P* | | 0.008 | 0.622 | 0.448 |
| Lymph nodes status | | | | |
| Negative | 40 | 2.45(1.73~3.36) | 2.06(1.41~2.79) | 17.93(16.23~21.84) |
| Positive | 50 | 3.46(1.87~5.26) | 2.32(1.57~3.34) | 20.08(16.11~25.66) |
| *Z* | | −2.233 | −1.017 | −1.024 |
| *P* | | 0.025 | 0.311 | 0.306 |
| Ki-67 | | | | |
| ≤14% | 33 | 2.43(1.75~4.33) | 1.96(1.48~2.73) | 18.28(15.96~22.25) |
| >14% | 57 | 2.86(1.81~3.96) | 2.34(1.54~3.06) | 20.06(16.37~23.87) |
| *Z* | | −0.590 | −0.891 | −0.450 |
| *P* | | 0.555 | 0.376 | 0.653 |

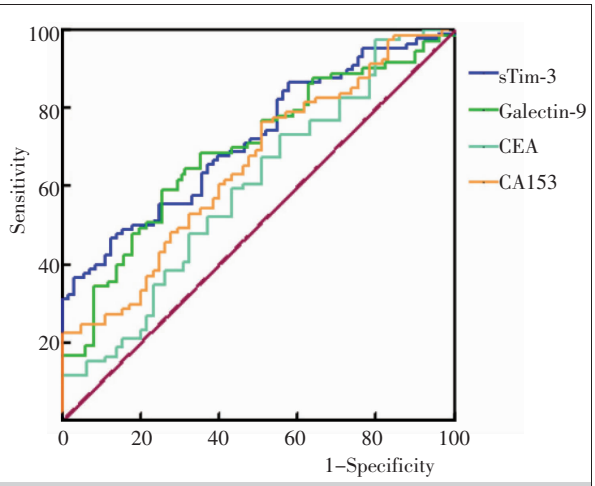


**Figure 1　Curve of sTim-3, Galectin-9, CEA and CA153 diagnosis for breast cancer**

## 3　讨　论

研究表明肿瘤在机体的免疫逃逸是肿瘤得以发生、发展、侵袭和转移的关键因素之一，因此，抑制性免疫检查点通路作为肿瘤免疫治疗的方向得到广泛研究应用。

免疫检查点分子 Tim-3 作为 T 细胞表面抑制性分子最初被发现在 Th1 细胞上高表达，然而，目前在 $CD8^+$T 细胞、调节性 T 细胞(Treg)、树突状细胞、自然杀伤细胞等其他淋巴细胞亚群以及肿瘤细胞中均发现 Tim-3 的表达[7]。多种实体肿瘤中的研究发现，Tim-3 高表达于 $CD8^+$ 肿瘤浸润性淋巴细胞(tumor-infiltrating lymphocytes，TIL)，促使 $CD8^+$T 细胞功能耗竭并诱导其凋亡，靶向阻断 Tim-3 后 $CD8^+$T 细胞恢复效应功能和增殖能力[8-9]。在非小细胞肺癌中 Tim-3 在肿瘤微环境中的调节性 T 细胞(Treg)的表达上调，$Tim\text{-}3^+$Treg 充当效应 T 细胞功能的有效抑制剂[10]，表明 Tim-3 充当抗肿瘤免疫的负性调节分子，降低机体免疫系统对肿瘤的杀伤，从而使肿瘤细胞发生免疫逃逸。本次研究发现，在乳腺癌患者血清 sTim-3 水平显著性高于体检正常人群，提示 Tim-3 可能参与乳腺癌的发生发展进程。ROC 曲线分析显示血清 sTim-3 对乳腺癌的诊断特异度要优于传统的乳腺癌标志物 CEA、CA15-3，其中 sTim-3 以 2.83 ng/ml 为临界值时，特异度为 92.75%，提示sTim-3 可作为乳腺癌血清学标志物。最近有研究发现 Tim-3 可通过 NF-κB/STAT3 信号通路直接促进乳腺癌细胞的增殖、迁移和侵袭，同时导致紫杉醇耐药的产生，乳腺癌组织中 Tim-3 的高表达提示预后不良[11]。此外，我们研究还发现，血清 sTim-3 表达水平与年龄、肿瘤大小、临床分期和腋窝淋巴结转移显著性相关($P$<0.05)。在大于 50 岁组、肿瘤大于 2 cm、临床分期晚、发生腋窝淋巴结转移病例中呈显著性升高，推测 Tim-3 能直接促进乳腺肿瘤组织的生长，并在肿瘤侵袭转移中发挥重要作用，提示血清 sTim-3 高表达可能与乳腺癌预后存在相关性。

Galectin-9 是半乳凝集素家族成员，作为 TIM-3 最早发现的配体，Galectin-9 特异性结合 Th1 上 Tim-3 IgV 结构域的碳水化合物基序并诱导 Th1 细胞的凋亡[12]。恶性实体瘤中，Galectin-9 通过结合 Tim-3 诱导 T 细胞耗竭或无能，减少效应因子干扰素-γ(IFN-γ)和肿瘤坏死因子-α(TNF-α)释放，进而阻断抗肿瘤反应，阻断 Tim-3/Galectin-9 信号通路可显著性增强肿瘤浸润性 $Tim\text{-}3^+$T 细胞的功能[13]。Galectin-9 是可溶性蛋白质，Seifert AM 等[14]的研究发现在胰腺导管腺癌中 Galectin-9 不仅存在于肿瘤细胞和免疫细胞中，同时在患者血清中高表达，作为疾病诊断的血清学标志物并与预后相关。我们研究发现，乳腺癌患者血清 Galectin-9 表达水平显著性高于正常体检人群，提示其在乳腺癌的发生发展中起一定作用。Galectin-9 与乳腺癌病理学资料均无显著性相关，但在临床分期晚，Ki-67 表达高，伴随腋窝淋巴结转移的肿瘤患者中表达有一定的升高趋势。Yasinska 等[15]研究也表明，乳腺癌组织中 Galectin-9 和 Tim-3 高表达，同时 Tim-3 和 Galectin-9 在乳腺癌细胞中共定位并形成复合物。Galectin-9 通过保护乳腺肿瘤细胞免受细胞毒性 T 细胞诱导的死亡从而使肿瘤得以逃避宿主的免疫攻击，证实了 Tim-3-Galectin-9 途径参与了乳腺癌的发生发展。ROC 曲线分析显示，Galectin-9 的曲线下面积为 0.692，以 2.01 ng/ml 为临界值，灵敏度(58.9%)和特异度(74.51%)均一般，因此 Galectin-9 可能并不适合作为单一的乳腺癌诊断指标。

CEACAM-1 是一种细胞跨膜糖蛋白，在细胞粘附、血管生成和肿瘤免疫抑制上发挥重要调节作用。研究发现 CEACAM-1 作为 Tim-3 的配体，能增强 Tim-3 分子的负性免疫调控功能，联合阻滞两者的

表达增强了抗肿瘤免疫应答。在大肠癌中,Tim-3 和 CEACAM-1 共表达介导 T 细胞耗竭,并作为大肠癌独立预后危险因素成为潜在的生物标志物[16-17]。Huajun 等[18]研究发现结肠癌患者血清中高表达 CEACAM-1,并有望成为较好的血清学诊断标志物。本文我们研究发现,乳腺癌患者血清 CEACAM-1 表达与正常体检组并无显著性差异,但与乳腺癌组织学分级相关,并随组织学分级升高而增高($P<0.05$);乳腺癌患者血清 CEACAM-1 在临床分期晚,Ki-67 表达更高,伴随腋窝淋巴结转移的肿瘤患者中表达有升高趋势,但差异无统计学意义($P>0.05$)。我们推测在初发性乳腺癌患者中,血清 CEACAM-1 并不会明显升高,但随着肿瘤进展可能会进一步表达。后续研究应增加晚期乳腺癌或者复发性转移性患者病例,探究 CEACAM-1 与乳腺癌预后的相关性。

综上所述,sTim-3 在乳腺癌患者血清水平显著性上调,并与临床病理学特征相关,可能成为乳腺癌的生物学标志物。Galectin-9 在乳腺癌患者血清水平上调,但与临床病理学特征无关,Tim-3/Galectin-9 可能参与了乳腺癌的发生发展。CEACAM-1 在乳腺癌患者血清水平与正常体检组相比无显著性差异,但与肿瘤组织学分级相关,Tim-3/CEACAM-1 在乳腺癌的发生发展中的作用有待进一步研究。由于乳腺癌不同亚型间存在较大的异质性,且本研究病例数较少,可能存在偏倚性,后续需加大样本量进一步验证分析。尽早弄清 Tim-3 及其配体 Galectin-9、CEACAM-1 在乳腺癌中的表达情况,有助于为 Tim-3/Galectin-9、Tim-3/CEACAM-1 通路在乳腺癌发生发展转移机制研究提供依据。

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