Tim-3在乳腺癌中的作用

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摘要 乳腺癌是女性中最常见的癌症, 死亡率极高。尽管乳腺癌的治疗方法取得了许多进展, 但其高度异质性和侵袭转移能力使得临床上迫切需要新的治疗策略与思路。随着免疫检查点封闭疗法的兴起, T细胞免疫球蛋白及黏蛋白结构域分子3(Tim-3)走进人们的视野。Tim-3作为免疫检查点分子, 在乳腺癌的发展中起着重要作用。Tim-3可用于乳腺癌治疗效果的评估, 抗Tim-3抗体及其他抑制剂对乳腺癌的治疗在临床前研究中已取得成效。该综述总结了有关Tim-3的表达机制及其在乳腺癌中的作用, 并讨论了Tim-3作为乳腺癌治疗靶点的基本原理以及Tim-3在乳腺癌中的潜在治疗方案。

关键词 Tim-3; 乳腺癌; 免疫检查点; 免疫治疗

The Role of Tim-3 in Breast Cancer

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Abstract Breast cancer is the most common cancer among women, with a very high mortality rate. Although many advances have been made in the treatment of breast cancer, its high degree of heterogeneity and ability of invasion and metastasis make the clinical urgent need for new treatment strategies and ideas. With the rise of immune checkpoint blocking therapy, Tim-3 (T cell immunoglobulin and mucin domain molecule 3) entered people's field of vision. Tim-3, as an immune checkpoint molecule, plays an important role in the development of breast cancer. Tim-3 can be used to evaluate the effect of breast cancer treatment. Anti-Tim-3 antibodies and other inhibitors have been effective in the treatment of breast cancer in preclinical studies. This review summarizes the expression mechanism of Tim-3 and its role in breast cancer, and discusses the basic principles of Tim-3 as a breast cancer treatment target and potential treatment options for Tim-3 in breast cancer.

Keywords Tim-3; breast cancer; immune checkpoint; immunotherapy

乳腺癌(breast cancer)是女性中最常见的恶性肿瘤, 每年影响超过150万名女性, 是女性癌症相关死亡的主要原因[1]。尽管对乳腺癌生物学和化学抗药性的认识不断提高, 早期诊断和综合治疗策略也不断进步, 但是乳腺癌一旦发展到了晚期, 在很大程度上仍然是难以治愈的疾病。因此, 探寻能够有效治疗乳腺癌的方法至关重要。

肿瘤微环境(tumor microenvironment, TME)在肿瘤的进展和预后中起着至关重要的作用。免疫系统通常具有识别和消除肿瘤细胞的能力。在TME中, 肿瘤通过降低抗原性和利用反馈抑制作用来削弱免疫细胞的抗肿瘤能力[2], 因此, 通过提高自身免疫系统并诱导抗肿瘤反应的肿瘤免疫疗法受到越来越多研究者的关注。Tim-3是一种新的免疫检查点分子,

收稿日期: 2021-01-21 接受日期: 2021-02-02

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Received: January 21, 2021 Accepted: February 2, 2021

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URL: http://www.cjcb.org/arts.asp?id=5521

能在各种免疫细胞上表达, 包括自然杀伤细胞、内皮细胞、巨噬细胞、树突状细胞等[3-4]。Tim-3通过调节这些免疫细胞的功能来影响免疫反应, 发挥其在免疫调节中的重要作用[5]。近年来, 关于Tim-3在癌症中的免疫作用已经成为研究的热点。本文综述了Tim-3的表达机制及其在乳腺癌中的作用, 并讨论了Tim-3作为乳腺癌治疗靶点的基本原理及潜在治疗方案, 希望为乳腺癌的预防和治疗提供新的方法或思路。

1 Tim-3的结构和功能

Tim-3是一种I型细胞表面糖蛋白, 包括一个N-端免疫球蛋白样结构域、一个带有*O*-连接糖基化和N-连接糖基化的黏蛋白结构域、一个单一的跨膜区, 以及一个带有酪氨酸磷酸化基序的细胞质区域[6]。Tim-3在IgV区域包含两个与之反向平行的 二硫键, 另外两个二硫键由四种非经典半胱氨酸组成。这些二硫键的存在稳定了Tim-3的IgV区域, 并将CC环与FG环排列成“裂缝”或“口袋”结构[7-8]。Tim-3编码基因*HAVCR2*, Tim-3的结构与甲型肝炎细胞受体同源, 位于人类基因组中的5q33.2, 该区域与哮喘、过敏和自身免疫相关[9]。Tim-3可分为可溶性Tim-3(soluble Tim-3, sTim-3)和膜结合Tim-3这两种形式。sTim-3(由金属蛋白酶ADAM10和ADAM17介导)主要从膜上脱落产生, 还有一部分来源于脾细胞[10-11]。

目前公认的Tim-3配体主要有四个。它们分别是半乳糖凝集素9(galectin-9, Gal-9)、高迁移率族蛋白B1(high mobility group box-1 protein, HMGB1)、磷脂酰丝氨酸(phosphatidylserine, PtdSer)和癌胚抗原细胞黏附分子1(carcinoembryonic antigen-related cell adhesion molecule 1, Ceacam-1)。Tim-3与不同细胞上的配体结合发挥不同的免疫调节作用(表1)。最先确定的第一个Tim-3配体Gal-9广泛分布于各个组织中。Gal-9与Tim-3结合可诱导辅助性T淋巴细胞1(T helper 1, Th1)和同种异体反应性$CD8^+$T细胞凋亡[12], 从而减轻自身免疫性疾病, 延长同种异体移植物存活时间。HMGB1在肿瘤浸润的树突状细胞(dendritic cell, DC)中高度表达。Tim-3与HMGB1结合的核酸竞争, 干扰核酸向DC内募集, 从而减弱对肿瘤相关核酸的先天免疫应答[13-15]。PtdSer与Tim-3的相互作用主要在凋亡小体的清除中起作用, 也可以促进抗原交叉呈递[16]。CEACAM-1被认为是一种新的Tim-3配体, 其通过形成顺式键(对应于在同一细胞上形成的异源二聚体)或反式键(这两种分子都

表1 Tim-3的配体及其在不同免疫细胞上的功能(根据参考文献[6]修改)

Table 1 Tim-3 ligands and their functions on different immune cells (modified from reference [6])

配体 Ligands	Tim-3的位置 Location of Tim-3	功能 Functions	参考文献 Reference
Gal-9	T cells	T cell failure	[18]
	$CD8^+$T cells	Dysfunction and apoptosis	[19]
	Treg	Cross regulation between Th17 cells and Treg cells	[20]
	Monocytes	Decrease phagocytic activity and HLA-DR expression	[21]
	Macrophages	M2 polarization	[22]
	NK	Enhance IFN-γ production	[23]
	Th1 cells	Th1 cell apoptosis	[24]
		Expanded granulocyte immunosuppression	[25]
		Promote the transfer of Th1/Th2 balance to Th2	[26]
HMGB1	$CD8^+$T cells	Prevent HMGB1-mediated T cell activation	[27]
	DCs	Interfere with the recruitment of nucleic acids to DC endosomes and prevent DC activation	[13]
		Inhibit the production of CXCL9 and reduce the complement of $CD8^+$T cells to TME	[28]
PtdSer	Macrophages	Eliminate apoptotic cells and prevent cross-expression	[29]
	DCs	Eliminate apoptotic cells and prevent cross-expression	[29]
CEACAM1	T cells	T cell failure	[30-31]
	$CD8^+$T cells	Inhibit the cis or trans immune response in $CD8^+$T cells	[28]

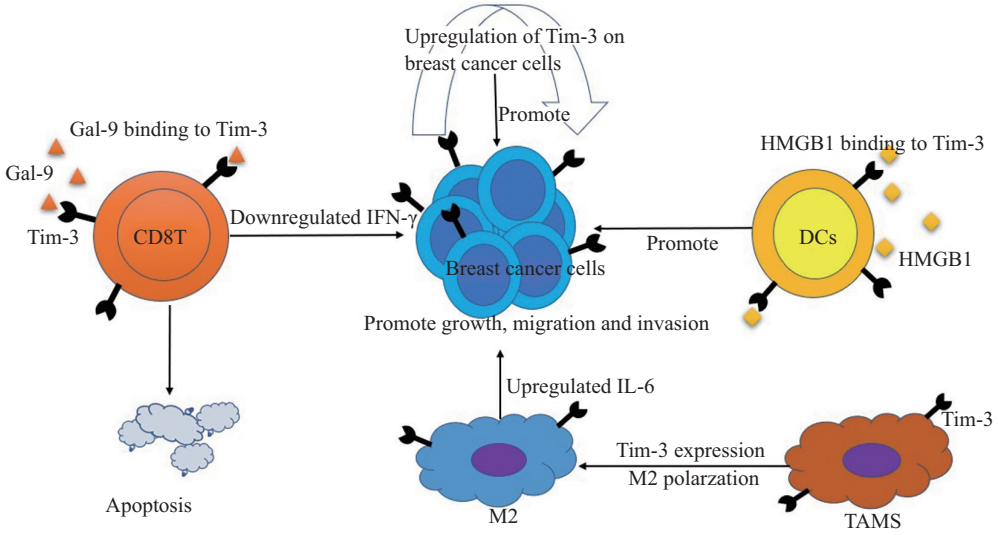
由不同的细胞表达)来维持Tim-3的稳定[17]。当Gal-9或CEACAM-1配体与Tim-3结合时, 产生的酪氨酸磷酸化释放BAT3, 使酪氨酸激酶(tyrosine-protein kinase, Fyn)与Tim-3的胞质结构域结合, 并传递抑制信号[16]。

2 肿瘤免疫微环境中的Tim-3对乳腺癌的免疫调节作用

肿瘤免疫微环境(tumorimmune microenvironment, TIME)在肿瘤进展中起着至关重要的作用。TIME包含肿瘤细胞以及多种免疫细胞, 包括肿瘤浸润的T细胞、树突状细胞、调节细胞和固有的自然杀伤细胞等。免疫抑制是TIME的主要特征[32]。Tim-3的表达增加或共表达被认为是效应T细胞(effector T cells, Teffs)衰竭的指标[33]。Tim-3的免疫抑制作用对乳腺癌的发生发展至关重要(图1)。

2.1 T细胞上Tim-3与乳腺癌

人体内的免疫机制大都是由T细胞介导的。$CD8^+$T细胞是肿瘤清除的关键介质。$CD8^+$T细胞可以直接作为效应细胞特异性杀死癌细胞, 故被称为细胞毒性T细胞(cytotoxic lymphocytes, CTL)。如果人体能够为肿瘤细胞产生足够的特异性CTL, 则癌细胞难以存活[34]。Tim-3的表达首先在$CD4^+$T细胞和$CD8^+$T细胞上被发现, Tim-3在肿瘤浸润淋巴细胞(tumor-infiltrating lymphocyte, TIL)中高表达。几项研究均表明, Tim-3水平在肿瘤浸润性T细胞中明显升高[35-37]。在乳腺癌中, Tim-3的水平与肿瘤浸润$CD8^+$T细胞、$CD4^+$T细胞以及DC密切相关[38], 且乳腺癌患者T淋巴细胞中Tim-3呈现高表达[39], 尤其是$CD8^+$T细胞上Tim-3的表达高于正常组织[40]。此外, 有研究表明白细胞介素-2(interleukin-2, IL-2)和白细胞介素-15(interleukin-15, IL-15)均可作为有效的共刺激信号, 增强乳腺癌的肿瘤浸润CD8T细胞增殖和干扰素-γ(interferon-γ, IFN-γ)的产生[41]。该研究将Tim-3配体Gal-9和Tim-3阻断抗体加入细胞培养物中。结果显示, 加入Gal-9显著降低了乳腺癌中肿瘤浸润CD8T细胞的增殖和IFN-γ的产生, 并大大提高了乳腺癌的肿瘤浸润CD8T细胞的凋亡, 而加入Tim-3阻断抗体可以恢复这些作用。此外, 加入IL-15与Tim-3的阻断抗体, 可促进乳腺癌的肿瘤浸



Gal-9和乳腺癌的肿瘤浸润CD8T细胞上Tim-3结合降低了CD8T细胞的增殖和IFN-γ的产生, 同时促进乳腺癌肿瘤浸润CD8T细胞的凋亡, 加重肿瘤负荷。DCs上的Tim-3与核蛋白HMGB1结合, 干扰核酸向DC内体的募集, 阻止DC的活化, 从而加重肿瘤负荷。乳腺癌细胞上Tim-3的过表达促进乳腺癌细胞自身的增殖、迁移和侵袭。肿瘤相关巨噬细胞(TAMs) Tim-3过表达促进TAM的M2极化, 进一步增加IL-6的分泌来促进乳腺癌细胞的生长、迁移和侵袭。

The combination of Gal-9 and Tim-3 on the tumor-infiltrating CD8T cells of breast cancer reduces the proliferation of CD8T cells and the production of IFN-γ, and at the same time promotes the apoptosis of breast cancer tumor-infiltrating CD8T cells and aggravates the tumor burden. Tim-3 on DCs binds to the nucleoprotein HMGB1, which interferes with the recruitment of nucleic acids to DC endosomes, prevents the activation of DCs, and increases tumor burden. The overexpression of Tim-3 on breast cancer cells promotes the proliferation, migration and invasion of breast cancer cells themselves. The overexpression of Tim-3 in TAMs (tumor-associated macrophages) promotes the M2 polarization of TAM and further promotes the IL-6 pathway to promote breast cancer cell growth, migration and invasion.

图1 肿瘤免疫微环境中的Tim-3在乳腺癌中的免疫和调节功能

Fig.1 The immune and regulatory functions of Tim-3 in the tumor immune microenvironment in breast cancer

润CD8T细胞增殖和IFN-γ的产生。这些实验均证明了Tim-3信号通路与乳腺癌的肿瘤浸润CD8T细胞的凋亡和IFN-γ产生有关, 并且参与了IL-2和IL-15共刺激过程。上述研究均提示, Tim-3可能通过对T细胞功能的调控, 来参与乳腺癌的发生发展。

2.2 非T细胞上Tim-3与乳腺癌

DC也是抗肿瘤免疫所必需的。Tim-3在肿瘤浸润的树突状细胞中的表达明显高于正常组织树突状细胞中的表达, 并且其表达较$CD8^+$T细胞中更早且更高[40]。DCs上的Tim-3先与核蛋白HMGB1相互作用, 后者抑制核酸募集进入DCs的内腔, 从而抑制先天免疫应答的信号传递并导致化疗后肿瘤负荷增加[42-43]。

巨噬细胞可以极化为两个不同的亚群M1和M2。M1激活可以促进炎症并抑制肿瘤, 而M2激活则可以抑制炎症并促进肿瘤。在乳腺癌中, M2巨噬细胞和Tim-3紧密相关[38]。研究表明, Tim-3的表达能够促进M2巨噬细胞的极化, 并增加IL-6的分泌[44]。该实验使用RAW264.7细胞证明STAT1是巨噬细胞中Tim-3的信号转接头, Tim-3通过抑制STAT1-miR-155信号轴来控制巨噬细胞极化。因此, Tim-3可能促进抑制性巨噬细胞表型的进展从而推动肿瘤的发展。

NK能够组成性表达Tim-3。Tim-3水平升高与NK细胞高浸润水平显著相关, 并且Tim-3可能调节乳腺癌中的NK细胞的浸润[38]。Tim-3阻滞似乎增强了循环NK细胞的溶细胞功能, 但Tim-3在使肿瘤浸润的NK细胞活力恢复方面的作用仍有待证明[45]。总之, 这些研究表明了Tim-3作为NK细胞上的检查点受体的潜力。

2.3 乳腺癌细胞上Tim-3与乳腺癌

除了调节免疫细胞功能外, Tim-3还具有直接调节肿瘤细胞的功能。已在恶性胸膜间皮瘤、透明细胞肾细胞癌、骨肉瘤等肿瘤细胞上检测到Tim-3的表达[46-48]。用蛋白质免疫印迹实验检测Tim-3在乳腺癌细胞中的表达, 发现Tim-3的下调显著抑制了乳腺癌细胞的增殖、迁移和侵袭, 同时促进了乳腺癌细胞凋亡。而Tim-3的过表达则促进乳腺癌细胞的增殖、迁移和侵袭, 并抑制乳腺癌细胞凋亡[49]。可见乳腺癌细胞上Tim-3表达对乳腺癌细胞的增殖、迁移和侵袭有直接调节作用。研究发现, 乳腺癌患者乳腺组织中Gal-9和Tim-3的表达水平显著高于健康人, 但是未观察到肿瘤细胞分泌Gal-9[50]。乳腺癌细胞表面的Gal-9能够保护乳腺癌细胞, 避免被细胞毒性T细胞诱导从而死亡[50]。这种通过抑制Tim-3/Gal-9病理生化途径, 使免疫系统能够攻击恶性肿瘤, 可作为乳腺癌的治疗靶标, 并且有研究发现乳腺肿瘤组织中程序性死亡受体1(programmed death 1, PD-1)、细胞毒性T淋巴细胞相关蛋白4(cytotoxic T lymphocyte-associated protein 4, CTLA-4)、Tim-3的上调与DNA和组蛋白修饰有关[51], 这提示, Tim-3表达水平可以通过对DNA或者组蛋白的修饰进行调节。Tim-3作为一个免疫检查点可为乳腺癌患者的治疗开辟新的途径。

3 Tim-3在乳腺癌中的诊断及预后

已经证明Tim-3可以作为实体瘤(例如宫颈癌、胃癌、结肠癌以及非小细胞肺癌和透明细胞肾癌)的预后标志物, Tim-3表达水平高则患者存活率降低[52]。在乳腺癌中, 研究发现乳腺癌肿瘤浸润性$CD8^+$T细胞的数量与原发肿瘤大小、淋巴结转移、乳腺癌分级有关[40], 且$CD8^+$T细胞对Tim-3的表达高于正常组织。另有研究评估了乳腺癌患者肿瘤引流淋巴结(tumor draining lymph nodes, TDLNs) T细胞中的Tim-3表达及其与疾病进展的关系, 其结果表明, Tim-3在乳腺TDLNs中由$CD4^+$T、$CD8^+$T和调节性T细胞表达, 并且在$CD4^+$T细胞和$CD8^+$T细胞上的表达主要与不良预后(例如更多的受累淋巴结或更高肿瘤等级)相关[53]。尽管Tim-3与不良的临床病理因素相关, 但其表达与乳腺癌的存活率提高也有关, 并且是三阴性乳腺癌(three-negative breast cancer, TNBC)独立的阳性预后因素[54]。与上述研究相同, BURUGU等[55]调查了3 992例乳腺癌组织中的Tim-3免疫组织化学表达, 发现Tim-3与PD-1和LAG-3的共表达与有利的预后相关。但也有研究表明, 抗Tim-3抗体可激活乳腺癌小鼠模型中的肿瘤内DC, 并能改善对紫杉醇化疗的反应[56]。TU等[38]进一步研究了包括Tim-3在内的免疫检查点与乳腺癌治疗结果之间的关联。结果表明, 这些检查点分子的上调与全身治疗的乳腺癌的高生存率有关。另有研究使用包括Tim-3在内的10种免疫标记物鉴定了乳腺癌患者的免疫调节蛋白表达, 并且设计了一种免疫复发评分(immune recurrence score, IRS), 可预测I~III期乳腺癌的复发情况[57]。由于Tim-3可能促进乳腺癌的发生和发展并影响肿瘤的微环境, 因此Tim-3可能有

利于乳腺癌的诊断, 并可以作为乳腺癌患者的独立预后因素。

关于Tim-3在乳腺癌中的诊断及预后大部分研究都是基于Tim-3在免疫细胞上的表达, 目前Tim-3在血清中的含量与乳腺癌的发生发展的关系尚未有文献报道。有研究发现慢性乙型肝炎病毒(HBV)感染患者的血清Tim-3水平显著高于健康对照组, 并且从无症状HBV携带者状态到肝细胞癌(hepatocellular carcinoma, HCC), Tim-3的表达水平逐渐升高[58], 并且肝病患者中可溶性Tim-3值与HCC阶段呈正相关[59], 这提示了, 血清Tim-3水平可能与肝癌的严重程度有关。乳腺癌患者血清Tim-3水平是否也与其病程相关? 我们所在的研究团队收集了30例健康人和70例乳腺癌患者的血清, 发现乳腺癌患者血清中的Tim-3水平高于正常人, 差异显著。血清中的Tim-3主要由金属蛋白酶ADAM10和ADAM17介导的脱落产生[60-61], 这提示了乳腺癌患者血清中的Tim-3水平可能反映了免疫细胞或者肿瘤细胞膜表面的表达量, 通过检测乳腺癌患者血清中Tim-3的含量, 可能有利于对乳腺癌的筛查诊断, 但血清中Tim-3水平与乳腺癌的进程关系仍需要进一步研究。

上述的研究均提示了, Tim-3可能有助于乳腺癌的诊断并且可作为乳腺癌的潜在预后生物标志物。

4 Tim-3用于治疗乳腺癌的潜在方法

在肿瘤微环境中, 受免疫检查点相互作用调节的T细胞效应功能普遍失调或过度表达, 从而导致T细胞抑制或者下调T细胞反应。因此, 阻断免疫检查点(共抑制信号)或促进共刺激信号可以恢复或放大用于癌症治疗的抗原特异性T细胞的反应。临床上可以利用抗Tim-3抗体来促进IFN-γ等细胞因子的分泌, 从而起到抑制肿瘤的作用。TIM-3/Gal-9信号通路可以通过抑制T细胞的免疫作用, 以促进T细胞的耐受来控制相关疾病的发生和发展。目前, 多数研究表明, 任何干预对其多种生物回路的影响决定了Tim-3的阻断治疗的效果, 包括对$CD4^+$T细胞和$CD8^+$T细胞的调节, 抑制$Tim\text{-}3^+$Treg以及抑制$CD8^+$T细胞产生IFN-γ等[62]。Tim-3的表达水平标志着实体和血液系统恶性肿瘤动物模型中$CD8^+$T细胞的抑制或功能异常[63-66]。在这些动物模型中, 已成功证明Tim-3途径阻断与PD-1途径阻断有着相似的抗肿瘤活性, 并且PD-1、CTLA-4联合阻断能够增加T细胞的产生, 降低Tregs的表达, 恢复T细胞的免疫应答, 从而提高机体的抗肿瘤免疫作用[67]。同时, 研究发现乳腺癌患者Tim-3和PD-1的mRNA表达量和蛋白表达量都偏高, 且Tim-3与PD-1的mRNA表达量呈正相关[68], 将Tim-3和PD-1联合阻断可以抑制肿瘤的发生、发展和转移。这些均证明了Tim-3阻断或者Tim-3与PD-1、CTLA-4等联合阻断对乳腺癌的治疗具有极大的前景。最新报道的拮抗配体阻断性抗Tim-3抗体M6903, 是一种完全的人源抗Tim-3抗体, 没有效应子功能, 对Tim-3具有高选择性和亲和力, 能阻止Tim-3与其三个配体(Gal-9、PtdSer和CEACAM1)的结合, 单一疗法可以增强T细胞的活化。抗Tim-3抗体的优化, 为肿瘤的临床治疗带来了更好的治疗效果[69]。当然, 除了抗Tim-3抗体, 与Tim-3结合的具有高亲和力和特异性的抗核酸酶的适配体也已经走进了人们的视野。适配体是一种能与特定靶分子结合的单链或肽分子, 三聚体形式的适配体有效地阻断了Tim-3和Gal-9的相互作用, 从而增强$Tim\text{-}3^+$T细胞的增殖和抗肿瘤细胞因子的分泌。Tim-3适配体的抗肿瘤作用均优于抗Tim-3单克隆抗体[70]。与单克隆抗体相比, 适配体具有低抗原性、低成本、可重复使用和易于用荧光染料标记等优势, 因此, Tim-3适配体是抗Tim-3抗体的潜在替代品。

此外, 有研究发现miR-149-3p有望与编码T细胞抑制剂受体*PD-1*、*Tim-3*、B和T淋巴细胞衰减器(B- and T-lymphocyte attenuator, *BTLA*)和*Foxp1*的mRNA的3′UTR结合。该研究用miR-149-3p模拟物处理$CD8^+$T细胞可减少$CD8^+$T细胞凋亡, 并下调编码*PD-1*、*TIM-3*、*BTLA*和*Foxp1*的mRNA。miR149-3p模拟处理后, T细胞增殖和指示T细胞活化增强的效应细胞因子(IL-2、TNF-α、IFN-γ)的分泌上调。此外, 用miR-149-3p模拟物进行治疗提高了$CD8^+$T细胞杀死目标4T1小鼠乳腺癌细胞的能力[71]。这些数据表明, miR-149-3p可以通过下调编码*PD-1*、*Tim-3*、*BTLA*和*Foxp1*的mRNA来逆转$CD8^+$T细胞的衰竭, 是乳腺癌的潜在抗肿瘤免疫治疗剂。

根据体细胞表面T细胞受体的类型, 可以将T细胞分为γδT细胞和αβT细胞。γδT细胞是可以用于过继细胞治疗的理想细胞, 是一群具有高增殖能力和肿瘤杀伤能力的同质细胞。然而肿瘤过继免疫疗法主要有两个障碍: 一是离体培养的γδT细胞在持续刺

激(抑制剂)作用下易于凋亡, 并且细胞毒性降低; 二是不能有效地聚集在肿瘤部位。针对这两个障碍, 最近有研究发现, γδT细胞在离体扩增过程中, Tim-3的表达水平明显上调, 并且这种上调导致了γδT细胞的功能障碍[72]。尽管γδT细胞对表现出高水平上皮细胞黏附分子(epithelial cell adhesion molecule, EpCAM)的乳腺癌细胞的杀伤能力增强, 但在双特异性抗体MT110(抗CD3×抗EpCAM)的应用下, γδT细胞上Tim-3的水平也进一步上调。抗体MT110可将T细胞重定向至靶细胞。此外, 这些Tim-3上调的γδT细胞对凋亡的敏感性增加。通过使功能异常的γδT细胞恢复活力并促进其在肿瘤部位蓄积, Tim-3抑制剂和MT110的联合使用可进一步增强过继输注的γδT细胞的抗肿瘤作用。这些结果为旨在结合检查点封闭和免疫细胞重新定向的新型抗肿瘤方案的设计提供临床指导意义。

Tim-3作为一种免疫检查点受体, 在肿瘤组织中能够选择性表达, 并且在多种免疫抑制机制中起着关键作用。抗Tim-3抗体、Tim-3适配体等其他形式的抑制剂为乳腺癌的治疗提供了治疗思路, 并且Tim-3有希望可以通过单一或与其他免疫检查点联合的方式对乳腺癌进行靶向免疫治疗。

5 前景与展望

Tim-3作为一种免疫检查点分子, 在乳腺癌的发展中起着至关重要的作用。 Tim-3有助于乳腺癌早期诊断并且可作为乳腺癌的潜在预后生物标志物。Tim-3通过介导效应T细胞的耗竭和凋亡, 增强Treg介导的免疫抑制, 并促进T细胞功能障碍和肿瘤相关巨噬细胞(tumor-associated macrophages, TAMs) M2极化来抑制抗肿瘤免疫力。Tim-3抑制剂在临床前研究中显示出抗乳腺癌功效。与其他抑制剂(PD-1、CTLA-4)显示出联合的抗肿瘤作用。但针对Tim-3及其相关途径的抗体的安全性和副作用仍然需要大量的大型动物实验和临床试验来进一步检查, 抗Tim-3抗体的靶向性也需要进一步改善。高度特异性和高效的Tim-3抑制剂(如Tim-3适合配体)对乳腺癌的治疗具有极大的前景。过继细胞治疗和基因编辑的免疫细胞也是具有巨大潜力的研究方向。因此, Tim-3在乳腺癌的诊断和治疗方面具有极好的发展前景, 改变传统的治疗方法, 将为乳腺癌患者带来更大的希望。

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