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·专家论坛·

T细胞免疫球蛋白黏蛋白分子-3在肿瘤免疫中的作用和机制

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[摘 要] 应用单克隆抗体阻断PD-1、CTLA-4等免疫检查点已在肿瘤免疫治疗中取得了一定成效,但尚有部分患者对免疫检查点阻断剂疗效不佳,其机制可能为存在其他抑制性旁路。T细胞免疫球蛋白黏蛋白分子-3(T cell immunolobulin and mucin-containing protein-3,TIM-3)是一种可表达于多种免疫细胞,并具有重要调控作用的免疫检查点分子。已有研究报道多种肿瘤外周血和肿瘤浸润性T细胞中存在TIM-3高表达,并与预后不良相关。抗肿瘤免疫中,高表达TIM-3的T细胞、DC及单核巨噬细胞,可抑制肿瘤免疫应答。临床前研究显示,抗TIM-3单抗联合抗PD-1单抗可发挥协同抗肿瘤效应。TIM-3单克隆抗体已进入临床试验阶段。然而,TIM-3在调控免疫细胞中的部分功能尚待阐明,进一步理解TIM-3的免疫调节机制有助于推动基于阻断TIM-3抗肿瘤免疫治疗的临床应用。

[关键词] 肿瘤免疫; 免疫检查点;T细胞免疫球蛋白黏蛋白分子-3
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Current understanding of the role of T cell immunoglobulin and mucin-containing protein-3 in cancer immunity

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[Abstract] The application of monoclonal antibodies to block immune checkpoints including PD-1, CTLA-4 has demonstrated a good efficacy in cancer immunotherapy. However, some patients poorly responded to these immune checkpoints blockers. One probable mechanism for this failure in igniting the antitumor effect was that other inhibitory molecules over expressed in these cases. As an immune checkpoint, T cell immunolobulin and mucin-containing protein-3(TIM-3) is widely expressed in a variety of immune cells, and palys an important role in the regulation of immune response. Many studies showed that lymphocytes from patient peripheral blood or tumor-infiltrating lymphocytes expressed high levels of TIM-3, which was associated with poor outcome. T cell, DC cell and mononuclear phagocytes with over-expressed TIM-3 showed significant inhibitory effects on antitumor immune response. In preclinical studies, combined blockade of TIM-3 and PD-1 with antibodies showed a synergistic effect on antitumor immunity. Clinical trials are underway to evaluate the safety and efficacy of TIM-3 monoclonal antibodies in cancer patients. However, the regulatory role of TIM-3 on immune cells has not been fully clarified, better understanding of the immune modulatory mechanism of TIM-3 helps to develop effective treatment strategy of blockade of TIM-3 in future clinical trials.

[Key words] cancer immunity; immune checkpoint;T cell immunoglobulin and mucin-containing protein-3
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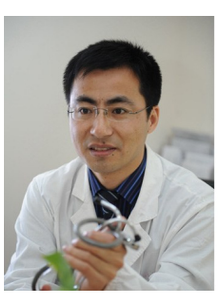

陶 荣,博士、主任医师,上海交通大学医学院附属新华医院血液科副主任,上海医学会血液学专业委员会委员。长期从事淋巴瘤的诊治研究,建立了MEDA化疗治疗晚期和复发难治性NK/T细胞淋巴瘤,对于弥漫性大B细胞淋巴瘤患者开展risk-adapted治疗,均取得良好疗效。基础研究中,发现NK/T细胞淋巴瘤存在多种生长因子及其受体的自分泌环路,并成为潜在的治疗靶点。发表SCI收录论文10余篇,获得专利2项。曾获上海交通大学医学院首届"上药杏林育才奖",入选上海市青年科技启明星计划,2015年入选上海市教育委员会高峰高原学科建设计划。

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免疫系统识别和清除肿瘤的过程中,可受到多种抑制性受体与配体的限制,此类分子相互作用构成的通路称为免疫检查点(immune checkpoint)。近年来,靶向免疫检查点的抑制剂得到发展,现已进入临床应用阶段[1]。靶向程序性死亡受体1(programmed death 1,PD-1)和细胞毒性T淋巴细胞抗原4(cytotoxic T lymphocyte-associated antigen-4,CTLA-4)等免疫检查点阻断剂已在多种肿瘤中显示出疗效[2]。PD-1阻断性单克隆抗体pembrolizumab和nivolumab已获FDA批准的用于多种进展期肿瘤,包括黑色素瘤[3]、非小细胞肺癌、霍奇金淋巴瘤[4-8]等。PD-1抗体在进展期肝癌[9]、肛管鳞状细胞癌[10]、卵巢癌[11]中也显示初步疗效。全人源化CTLA-4抗体ipilimumab是第一种免疫检查点抑制剂,Ⅲ期临床试验[12-13]结果显示,ipilimumab可提高转移黑色素瘤患者总体生存,接受ipilimumab治疗的患者中,20%可达到长期生存。尽管PD-1及CTLA-4抗体进入临床后取得的成功令人振奋,但仍有部分患者因存在多种免疫检查点发挥免疫抑制效应,故对阻断单靶点药物疗效不佳。因此探索靶向多种免疫抑制通路的策略,是提高免疫检查点阻断性抗体疗效的关键。

目前关于多种免疫检查点阻断剂联合应用的研究中,T细胞免疫球蛋白黏蛋白分子-3(T-cell immunoglobulin and mucin-containing protein-3,TIM-3)是前景较好的靶点之一。TIM-3为TIM家族成员,该家族包括在人类表达的TIM-1、TIM-3和TIM-4和在小鼠表达的TIM-1-8。TIM-3可表达于Th1、Th17、$CD8^+$T细胞和多种髓系细胞[14-16]。多项研究[17-18]显示,TIM-3可通过调节多种免疫细胞,抑制免疫应答但仍有部分机制尚未阐明。

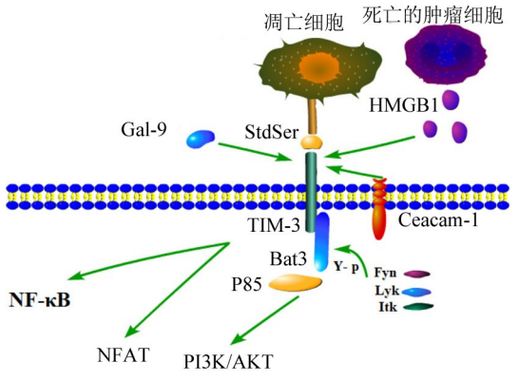
本文对TIM-3在免疫调控中的机制和肿瘤免疫中所发挥的作用进行讨论,并进一步探讨TIM-3作为肿瘤免疫治疗靶点的潜在价值。

1 TIM-3的分子结构、配体和信号通路

Monney等[16]首次报道了TIM-3表达于Th1细胞膜表面,并初步阐述了TIM-3分子在自身免疫性疾病中调控巨噬细胞功能所发挥的作用。TIM家族为Ⅰ型穿膜蛋白,其成员结构相似,均包含可变区免疫球蛋白结构域(IgV)、胞外糖基化黏蛋白样结构域和单次穿膜结构域[19-23]。除TIM-4外,所有TIM分子均包含一个带有磷酸化基序的胞质尾区[19-25]。

目前已发现4种配体可通过与TIM-3 IgV区结合发挥作用[26],包括凝集素半乳糖苷-9(galectin-9,Gal-9)、磷脂酰丝氨酸(PtdSer)、高迁移率族蛋白B1((high mobility group box-1 protein,HMGB1)和癌胚抗原相关细胞黏附分子1(carcinoembryonic antigen related cell adhesion molecule 1,Ceacam-1)。Gal-9是第一个被发现可结合于TIM-3的配体,可通过促进钙离子流入胞内,诱导Th1细胞凋亡[17]。TIM-3的另一配体PtdSer可暴露于凋亡细胞胞膜表面,与TIM-1、TIM-3、TIM-4 IgV结构域结合,介导凋亡细胞吞噬[27],促进凋亡小体清除和树突状细胞(DCs)抗原交叉提呈[28]。TIM-3的第三种配体为HMGB1。肿瘤浸润DCs高表达TIM-3可与死亡肿瘤细胞释放的核酸竞争性结合HMGB1,抑制核酸激发的固有免疫应答[29],导致固有免疫激活和促炎因子释放水平下降。表达于细胞膜的ceacam-1是新近发现的TIM-3配体,ceacam-1和TIM-3可共表达并形成异源二聚体,对T细胞免疫应答具有负调控作用[30]。

TIM-3处于T细胞信号通路的近端,在T细胞受体(TCR)信号通路中具有正向和负向双重效应。在Jurkat细胞系中,瞬时表达TIM-3可激活TCR信号转导通路中的NFAT和NF-κB,上述效应需通过TIM-3 256和263位的酪氨酸磷酸化实现[20]。Src激酶家族成员Lck、Fyn和ItK可与TIM-3磷酸化酪氨酸结合[20]。TIM-3胞质区磷酸化的酪氨酸可募集p85蛋白,进一步激活PI3激酶。TIM-3也可抑制TCR近端信号,在$TIM-3^+CD8^+$效应T细胞中,Gal-9可诱导TIM-3和磷酸化CD45、CD148共定位,抑制TCR信号转导[31-32]。稳定表达TIM-3的Jurkat细胞可抑制TCR介导的NF-κB和NFAT激活[32]。Gal-9与TIM-3结合后,256位和263位酪氨酸发生磷酸化,结合于TIM-3胞质尾区的bat-3从TIM-3释放[33]。Bat-3可逆转TIM-3在TCR信号通路中的负调控效应,机制可能为招募激活的Lyk或阻断Fyn与TIM-3结合[26,33]。综上,TIM-3在TCR信号通路的效应与细胞组分或其募集配体有关(图1)。



PtdSer:磷脂酰丝氨酸;HMGB1:高迁移率族蛋白B1;Gal-9:凝集素半乳糖-9;Ceacam-1:癌胚抗原相关细胞子黏附分子;Y-p:酪氨酸磷酸化

图1 TIM-3配体及信号通路模式图

2 TIM-3在肿瘤免疫中的作用

2.1 TIM-3对T细胞的调控

TIM-3下游信号通路可通过多种机制直接调控Th1和$CD8^+$T细胞功能。诱导Th1细胞表达TIM-3可直接触发细胞凋亡,从而抑制Th1细胞介导的免疫应答[17]。肿瘤发生转移的黑色素瘤患者中,肿瘤抗原特异性$CD8^+$T细胞和$CD8^+$肿瘤浸润性淋巴细胞(tumor infiltrating lymphocyte,TIL)高表达TIM-3。肺癌患者$TIM\text{-}3^+CD8^+$TIL中表达IFN-γ比例较$TIM\text{-}3^-CD8^+$TIL少,应用TIM-3mAbs可恢复T细胞抗肿瘤效应[34-36]。这些结果支持TIM-3在肿瘤免疫抑制状态形成中T细胞耗竭这一环节中所发挥的作用。肿瘤患者$CD4^+$T细胞中也存在TIM-3表达升高[35-36]。值得注意的是,CD4+$TIM\text{-}3^+$肿瘤浸润性淋巴细胞中$Foxp3^+$细胞比例较高,提示肿瘤微环境中TIM-3可能影响Treg细胞功能[36]。

2.2 TIM-3对NK细胞的调控

有报道[37]显示,TIM-3是自然杀伤性(natural killer,NK)细胞的抑制性受体,人类成熟NK细胞中TIM-3呈高表达,未成熟NK细胞中TIM-3表达水平不一;经IL-12、IL-15、IL-18刺激后,可提高NK细胞TIM-3表达水平,高表达TIM-3的NK细胞的功能效应包括细胞因子释放和细胞毒等更强,但TIM-3可抑制NK细胞介导的细胞毒作用,提示TIM-3可能通过结合一种或多种配体对NK细胞活性产生不同的调控作用。多项研究[38-40]显示,TIM-3可抑制NK细胞介导的免疫应答。另有部分研究显示,TIM-3可正向调节NK细胞细胞因子表达,NK细胞在低剂量Gal-9作用后IFN-γ表达水平增加,敲除TIM-3后IFN-γ表达水平下降。最近,研究[41]报道了TIM-3/Gal-9通路诱导NK细胞产生抗炎因子及调节Treg细胞间接发挥免疫抑制效应。综上,TIM-3可能对NK细胞功能具有激活和抑制双重调控作用,具体调控方向取决于不同的生理和病理状态。

2.3 TIM-3对髓系免疫细胞调控

除淋巴细胞外,TIM-3也可表达于多种髓系细胞(DCs、单核细胞和巨噬细胞),并在调节固有免疫细胞介导的抗肿瘤免疫中发挥重要作用[42]。DCs可通过TIM-3结合PtdSer介导摄取凋亡细胞和交叉提呈抗原,这些作用均可被TIM-3 mAbs抑制[28]。尽管有证据显示TIM-3在调节DCs功能中为正向调节,但也有一些研究显示在肿瘤微环境中,TIM-3在DCs中传递抑制性信号。在肿瘤组织中,HMGB1可与肿瘤来源的核酸结合以入胞形式进入DCs 并激活DCs固有免疫应答。而肿瘤微环境中,TIM-3可高表达于DCs,竞争性结合HMGB1,减弱核酸在抗肿瘤免疫中的激活效应[43]。TIM-3在DCs中所发挥的具体效应可能取决于DCs种类和相关特异性配体。

有报道[16]显示,TIM-3可促进和抑制单核和巨噬细胞的双重功能。应用TIM-3 mAbs可提高激活巨噬细胞数量并加重自身免疫性疾病。TIM-3持续表达于$CD14^+$单核细胞,阻断TIM-3信号或沉默TIM-3表达可显著提高IL-12和IL-10产生,降低PD-1表达[44]。

近期研究[45]报道,TIM-3可通过抑制核转录因子红细胞系相关因子-2(Nrf2)通路抑制巨噬细胞功能。髓系细胞的表型与肿瘤进展高度相关,TME中肿瘤相关巨噬细胞(tumor associated macrophages,TAMs)和髓样抑制细胞显著数量升高。TIM-3可在多种肿瘤TAMs中表达[46-47]。上述研究结果均提示TIM-3可在髓系免疫细胞介导的免疫应答中主要发挥抑制效应。

3 肿瘤免疫治疗中靶向TIM-3的应用

TIM-3可高表达于多种肿瘤外周血和TIL中的肿瘤抗原特异性T细胞,提示TIM-3在抗肿瘤免疫中发挥重要作用。TIM-3上调与黑色素瘤患者肿瘤抗原特异性$CD8^+$T细胞耗竭有关,应用TIM-3 mAbs后可逆转肿瘤诱发的T细胞耗竭[34]。在非小细胞肺癌患者中,TIM-3主要表达于肿瘤浸润性$CD4^+$和$CD8^+$T细胞,而外周血T细胞表达水平极低。此外,在$CD4^+$TIL中,TIM-3倾向于在$Foxp3^+CD4^+$Treg细胞中表达,且$CD4^+TIM\text{-}3^+$TIL表达比例高的患者生存情况差[35]。近期,Granier等[48]报道了肾细胞癌患者肿瘤浸润性$PD\text{-}1^+CD8^+$ T细胞TIM-3表达为阳性,则预后更差,TIM-3、PD-1共表达患者疾病更具侵袭性。此外,在肝癌、宫颈癌、结肠癌、卵巢癌[49]、非小细胞肺癌[50]、头颈部肿瘤[51]、胃癌[52]、食管癌[53]、前列腺癌[54]、非霍奇金淋巴瘤[55]的TIL和肿瘤抗原特异性T细胞中也观察到了相似的结果,TIM-3高表达的患者预后更差。

在临床前研究中,应用TIM-3 mAbs可产生多种抗肿瘤效应。已在小鼠肿瘤模型CT26结肠腺癌、4T1乳腺癌和B16F10黑色素瘤中发现TIM-3在TIL 中高表达[36]。单独应用TIM-3 mAbs对CT26荷瘤小鼠肿瘤生长抑制作用不显著,但TIM-3和PD-1抗体联合使用抗肿瘤效果显著优于单独使用PD-1 mAbs[36]。在WT3肉瘤、TRAMP-C1前列腺肿瘤、MC38和CT26结肠腺癌小鼠模型中,注射TIM-3 mAbs可不同程度上减慢肿瘤进展;该研究中同样发现,TIM-3 mAbs联合CTLA-4 mAbs或联合PD-1 mAbs抗肿瘤效应明显增强[56]。在头颈部肿瘤组织中提取TIL经PD-1 mAbs处理后,TIM-3表达可上调,且TIL对PD-1 mAbs反应

减弱;在动物模型中也可观察上述现象,并可由TIM-3 mAbs逆转,恢复TIL对PD-1 mAbs治疗反应[57]。最近,Zhou等[58]报道了在体外实验中,单独应用TIM-3 mAbs可改善肝细胞肝癌患者肿瘤TIL功能。有研究[59]显示,NK细胞肿瘤杀伤功能也可被TIM-3 mAbs加强,在TIM-3 mAbs处理后,NK细胞清除转移性黑色素瘤细胞效应增强。上述研究均支持TIM-3可作为肿瘤免疫治疗的新靶点,尤其是采用TIM-3 mAbs联合PD-1或CTLA-4 mAbs治疗方式,将有望进一步提高现有靶向免疫检查点治疗肿瘤的疗效。

目前已有多项关于PD-1联合TIM-3 mAbs临床试验正在开展,其中3项用于治疗进展期实体瘤,包括1项Ⅰ-Ⅰb/Ⅱ期、开标、多中心临床试验(NCT02608268)和2项Ⅰ期临床试验(NCT02817633、NCT02817633)和1项用于治疗急性髓系白血病/高危骨髓增生异常综合征的Ⅰ期临床试验(NCT03066648)[60]。

4 结　语

目前,越来越多的证据显示TIM-3在抗肿瘤免疫中发挥负调控作用。TIM-3的诸多特点使其适合作为新一代免疫治疗的理想靶点。首先,TIM-3在肿瘤浸润性T细胞相对高表达,靶向TIM-3治疗特异性较高。此外,TIM-3下游所涉及的信号通路与PD-1和CTLA-4具有较大差异,单独靶向TIM-3或联合PD-1和CTLA-4单抗为现有靶向肿瘤免疫检查点治疗提供了新的思路。

阻断TIM-3提高细胞介导的抗肿瘤免疫应答已在多个研究中得到证实。TIM-3 mAbs联合其他免疫治疗药物具有协同效应。然而,由于TIM-3可同时表达于髓系细胞和淋巴细胞,TIM-3 mAbs体内实验抗肿瘤活性的确切细胞生物学机制尚未完全阐明。鉴于TIM-3具有双向调节免疫应答的作用,进一步探索TIM-3在不同类型细胞和肿瘤病理生理状态下所发挥的作用,对于靶向TIM-3的临床应用极其重要。

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