

靶向TGF- β 的肿瘤治疗策略研究进展

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Research Progress on Tumor Treatment Strategies Targeting TGF- β

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Abstract: The TGF- β signaling pathway affects various biological processes of cancers, including proliferation, invasion, metastasis, angiogenesis, and immune escape. Currently, multiple drugs targeting this pathway are in clinical trial stage, which involve three aspects of TGF- β , namely, production, activation, and signal transduction. Based on current evidence, the therapeutic effect of TGF- β monotherapy on advanced solid tumors is limited. Combination therapies that show promising results include combination with PD-1 antibodies, and combination with radiotherapy and chemotherapy. New combination therapies, such as CAR-T therapy modified with TGF- β II, are also emerging in clinical research. This article systematically reviews the therapeutic strategies targeting TGF- β to provide research basis and ideas for the development of drugs targeting the TGF- β pathway.

Key words: TGF- β ; Cancer; Therapeutic strategies; Tumor immune environment

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摘要: TGF- β 信号通路影响肿瘤的多种生物学过程, 包括肿瘤增殖、侵袭、转移、血管生成和免疫逃逸。目前已有多种靶向该通路的药物处在临床试验阶段, 这些药物涉及TGF- β 的生成、活化和信号转导三方面。基于当前的证据, TGF- β 单药对晚期实体瘤的治疗效果有限。联合治疗在临床试验中展现出具有应用前景的结果, 如联合PD-1抗体、联合放疗等。新的联合治疗方式也在临床研究中崭露头角, 如TGF- β II修饰的CAR-T治疗等。本文系统梳理了靶向TGF- β 的治疗策略, 以期对靶向TGF- β 的药物研发提供依据和思路。

关键词: TGF- β ; 肿瘤; 治疗策略; 肿瘤免疫微环境

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0 引言

转化生长因子- β (Transforming growth factor- β , TGF- β) 是调节肿瘤微环境的重要分子, 可由肿瘤相关成纤维细胞、间充质干细胞、血管内皮细胞、淋巴样上皮细胞和周细胞等分泌^[1-2]。哺乳动物TGF- β 的同源异构体包括TGF- β 1、TGF- β 2和TGF-

β 3, 其中, TGF- β 1的表达在肿瘤微环境中显著上调^[3]。TGF- β 基因直接编码的蛋白是一种由N端的信号肽、C端的成熟TGF- β 多肽和中间的前体片段三部分组成的TGF- β 前体, 在分泌过程中, 成熟的TGF- β 二聚体与其前体片段相关联, 组成无活性的潜在TGF- β ^[4]。潜在TGF- β 主要以与细胞基质中的潜在TGF- β 结合蛋白^[5]或者细胞膜上的糖蛋白A重复优势蛋白 (Glycoprotein-A repetitions predominant protein, GARP)^[6]结合两种形式存储, 需要被激活后才能与TGF- β 受体结合传递相关信号, 进而行使相关生物学功能。TGF- β 的激活主要受整合素、酸、活性氧、蛋白酶等调控^[7]。活化的TGF- β 分子与其受体TGF- β R II结合后会招募TGF- β R I, 磷酸化后的TGF- β R I进一步磷酸化下游介质来调节基因转录^[8]。一般认为TGF- β 在肿瘤形成的早期是一个

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抑癌基因，在肿瘤发展的晚期是一个促癌基因。在肿瘤晚期，TGF- β 除了能促进肿瘤的形成、增殖、侵袭和转移，还具有重塑免疫微环境的功能。TGF- β 分子可抑制CD8 T细胞的细胞毒功能^[9]、诱导CD4 T细胞向Treg转化^[10]，以及诱导内皮细胞和成纤维细胞向肿瘤相关成纤维细胞转变^[11]。针对TGF- β 通路的不同阶段，靶向TGF- β 的治疗策略主要包括：靶向TGF- β 的产生、激活、信号转导以及联合治疗。靶向TGF- β 产生的反义核苷酸类药物自从2011年Trabedersen在II期临床试验疗效不佳后鲜有进展^[12]，靶向TGF- β 的激活、信号转导和联合治疗的策略近期取得了一定程度的进展，但还存在着疗效较差、缺乏预后标志物等问题。深入理解各种药物的作用机制，有助于开发更好的靶向TGF- β 的治疗策略。本文主要对近年取得重要进展的靶向TGF- β 的肿瘤治疗策略进行综述，以期开发新的靶向TGF- β 的治疗策略提供思路。

1 靶向TGF- β 激活的药物

GARP是LRRC32基因编码的I型跨膜蛋白，分子量为72 kDa，主要在调节性T淋巴细胞（Regulatory T cells, Tregs）、活化的B细胞和血小板上表达。该分子是潜在TGF- β （Latent TGF- β , LTGF- β ）的对接受体。在整合素等物质的作用下，LTGF- β 从GARP/LTGF- β 复合物中释放出来并被激活^[13]。因此，靶向GARP/LTGF- β 的抗体能抑制TGF- β 的激活。2020年，de Stree等^[14]发现了靶向Treg源性的GARP能有效诱导肿瘤消退。目前，针对该靶点的药物走在最前列的是Livmoniplimab。Livmoniplimab是一款人源化抗GARP/TGF- β 1单抗。在一项治疗晚期实体瘤的I期临床试验中，Livmoniplimab联合抗PD-1抗体Budigalimab在接受铂类药物和免疫检查点治疗耐药后的尿路上皮癌队列中有可控的安全性和较好的疗效，其ORR为18%（8/45），并且在一部分患者中可观察到持续获益^[15]。目前，该联合方案治疗晚期肝细胞癌（Hepatocellular carcinoma, HCC）的临床试验（NCT05822752和NCT06109272）正在进行中。

SRK-181是一种靶向潜在TGF- β 的全人源化IgG4抗体，通过抑制TGF- β 的激活发挥抗肿瘤作用。因为该药只特异性结合TGF- β 1，与泛TGF- β 抑制剂相比，该药在动物模型中具有较弱的心脏毒性和血液毒性^[14,16]。在抗PD-1治疗耐药的晚期实体瘤患者中，SRK-181联合Pembrolizumab展现出较好的疗效和可控的安全性。在肾透明细胞癌和头颈鳞癌患者

中，ORR分别为20%和33.3%，但在非小细胞肺癌患者中ORR为0^[17]。目前，靶向GARP的药物有望在部分癌种中成为PD-1/PD-L1单抗的新搭档。

2 靶向信号传递的小分子抑制剂及抗体

2.1 TGF- β 中和抗体

Fresolimumab是一款靶向三种TGF- β 亚型的中和抗体。多线治疗后的转移性乳腺癌患者在接受放疗和Fresolimumab联合治疗后，高剂量组（ $n=12$ ）较低剂量组（ $n=11$ ）中位OS显著延长（16 vs. 7.57个月，HR: 2.73），但最佳疗效只有3例患者获得SD^[18]。3~4级不良反应的发生率为30.4%，主要不良反应类型为乏力、肝损伤和贫血。其他两款靶向TGF- β 的单克隆抗体NIS793^[19]和SAR439359^[20]对晚期实体瘤的疗效也十分有限。不同的是，NIS793只对TGF- β 1和TGF- β 2有较高的亲和力，具有可控的毒性，而SAR439359对三种TGF- β 亚型都有较高的亲和力，有致死性血液不良反应的发生且主要发生在肝癌患者。

2.2 靶向TGF- β 受体的小分子抑制剂

目前，有多种靶向TGF- β RI的小分子抑制剂问世，其中Galunisertib（LY2157299）具有较好的安全性，在临床试验阶段进展较快。Galunisertib联合抗血管药物索拉非尼在晚期肝癌患者中展现了具有前景的疗效和可控的毒性。在既往接受过索拉非尼治疗的149例HCC患者中，基线时甲胎蛋白水平较低（ <1.5 ng/ml）的患者OS显著改善（中位OS为16.8 vs. 7.3个月）^[21]。一项关于Galunisertib联合索拉非尼一线治疗晚期HCC的研究中，Galunisertib高剂量组（44例）中位OS为18.8个月，略高于索拉非尼的历史数据^[22]。来自日本的Galunisertib联合索拉非尼治疗HCC的1b期研究取得了相似的结果^[23]。但Galunisertib与抗VEGF2单抗Ramucirumab联合治疗晚期肝细胞癌时疗效并不优于单药Ramucirumab^[24]。初步研究结果表明，在Galunisertib联合抗血管治疗时，抗血管药物的选择以及根据肿瘤标志物筛选优势获益人群是需要考虑的重要问题。在一项局部晚期直肠癌患者新辅助治疗的二期单臂临床研究中，Galunisertib联合放化疗作为新辅助治疗方案将病理CR率提高到了32%，而历史数据只有8%~13%^[25]。Galunisertib联合抗血管治疗和联合放化疗分别在肝癌和直肠癌中取得一定的疗效，但联合免疫检查点抑制剂在NSCLC^[26]和胰腺癌^[27]等晚期实体瘤的治疗中却未见显著疗效。

Vactosertib是一种新的TGF- β RI的一种小分子

抑制剂,与Galunisertib相比,Vactosertib对骨肉瘤细胞系有更低的 IC_{50} ,对p-Smad2有更强的抑制能力^[28]。在临床研究中,Vactosertib联合帕博利珠单抗治疗33例既往经治的微卫星稳定型结直肠癌患者显示出良好的疗效,ORR达到15.2%,同时安全性良好^[29]。

IMC-TR1(又称作LY 3022859)是礼来公司研发的一种抗TGF- β R II的单克隆抗体药物,在IMC-TR1治疗晚期实体瘤的I期临床试验中发现其可引起不可控的细胞因子释放综合征^[30]。因为靶点的安全性问题,后续少有靶向TGF- β R II的药物问世。

3 TGF- β 与PD-1/PD-L1联合治疗策略

TGF- β 信号与PD-1/PD-L1信号对肿瘤的抑制机制互补^[4,31-32],因此,同时阻断TGF- β 和PD-1/PD-L1信号可能会增强抗肿瘤效果。TGF- β 与PD-1/PD-L1联合治疗策略包括联合使用抗TGF- β 与抗PD-1/PD-L1抗体和双靶点融合蛋白两种形式。目前双药联合的治疗策略在实体瘤治疗上安全可控,但疗效十分有限^[31]。PD-L1高表达的肿瘤微环境中,TGF- β 也高表达,在这种情况下,以双靶点药物同时抑制PD-L1和TGF- β 可能取得比双药联合治疗更好的疗效。临床前研究证实,在小鼠动物模型中,TGF- β /PD-L1融合蛋白疗法优于二者单独使用和联合使用^[33-35]。基于良好的临床前结果,多种TGF- β /PD-L1融合蛋白疗法逐渐问世,但目前尚无成功的三期临床试验。

M7824是由默克公司研发的全球首个获批临床试验的TGF- β /PD-L1双靶点药物,其主要结构包括抗PD-L1抗体端和TGF- β R II胞外结构。尽管该药在多种实体瘤的I期临床试验中展现了较好的安全性和有效性,但因为疗效有限,默克公司先后终止了多项II期和III期临床试验,现在仍有M7824联合其他药物治疗晚期实体瘤的临床试验正在进行中^[36]。

SHR-1701是一种由靶向PD-L1的IG4的单克隆抗体和TGF- β R II胞外结构域组成的双靶点药物。该抗体由恒瑞医药自主研发,是目前看来最有希望的TGF- β 双靶点药物。在SHR-1701治疗不可切除的III期非小细胞肺癌的II期临床研究中^[37],接受SHR-1701联合化疗新辅助治疗的患者诱导后的ORR为58%,18个月无事件生存率为56.6%,27例(25%)患者接受了手术治疗,均达到R0切除,其中,主要病理缓解率(Major pathologic response, MPR)为44%,完全病理缓解率(Complete pathologic response, pCR)为26%。而PD1/PD-L1抗体联合化

疗治疗可切除III A~III B期非小细胞肺癌的MPR率为27.3%~48.5%,pCR率为10.2%~24.8%。SHR-1701治疗胃或胃食管结合部癌、宫颈癌和非鳞非小细胞肺癌的三期临床研究正在进行。除M7824和SHR-1701外,还有多款PD-L1/TGF- β 双靶点药物处在临床前或者I期临床试验阶段^[38]。

4 细胞治疗

近年来,细胞治疗(如CAR-T)在血液肿瘤中得到了很好的发展,但在实体瘤治疗中面临着浸润困难和免疫耗竭等问题^[39]。一些研究设计了靶向TGF- β 的CAR-T和TCR-T,大多是对TGF- β R II进行突变设计。C-CAR031是一种靶向GPC3的TGF- β R II DN修饰的四代自体CAR-T。在一项肝细胞癌的I期临床研究^[40]中,24例GPC3阳性的至少一线治疗进展后的肝细胞癌患者接受了不同剂量的CAR-T细胞治疗。在22例可评估疗效的患者中,PR率50%(11/22),DCR为90.9%。mPFS为4.27个月,mOS尚未达到。另一个靶向GPC3的TGF- β R II DN修饰的CAR-T细胞治疗肝细胞癌的I期临床试验(NCT06084884)也在进行中。

TCR-T是治疗实体瘤的重要手段,但在临床实践中也存在肿瘤浸润差和免疫耗竭等问题^[41]。对TGF- β 通路的处理是增强TCR-T疗效的重要方法。今年ASCO会议有报道TGF- β R II敲除的TCR-T在临床前研究中展现了较好的抗肿瘤功能^[42],一项靶向KRAS G12D的TGF- β R II敲除的TCR-T I期临床试验(NCT06218914)已经启动,见表1。

5 展望

TGF- β 通路理论上是抑制抗肿瘤免疫的重要因素,靶向该通路的治疗策略不断出现,但也面临一些问题亟待解决。目前,靶向TGF- β 激活的策略中,Livmoniplimab联合PD-1抗体在尿路上皮癌和HCC患者中可能具有一定的发展前景。SRK-181联合Pembrolizumab可能在肾透明细胞癌和头颈鳞癌中有一定疗效。靶向TGF- β 的单克隆抗体疗法尚无较好的疗效,靶向TGF- β R II的策略可能会有较高的毒性。靶向TGF- β R I的小分子抑制剂中,Galunisertib与索拉非尼联合治疗晚期HCC以及Galunisertib联合放疗对局部晚期直肠癌可能会有临床获益。Vactosertib联合免疫治疗可能会对结肠癌有一定的治疗效果。PD-L1/TGF- β 类的双靶点药物理论上能取得1+1>2的治疗效果,但实际上却效果不一。不同的靶向TGF- β 的治疗策略对肿瘤的治疗效果可能与肿

表 1 靶向TGF-β药物的特点和临床研究
Table 1 Features and clinical trials of drugs targeting TGF-β

Class	Targets	Representative drugs	Representative clinical trials	Features
Activation	GARP	Livmoniplimab	Urothelial carcinoma (ORR 18%), Phase 1 ^[15]	Selective inhibition of TGF-β1 produced by GARP positive Tregs Targeting latent TGF-β to inhibit the activation of TGF-β
	LTGF-β	SRK-181	Renal cell carcinoma (ORR 20%), Head and neck squamous cell carcinoma (ORR 33%), Phase 1 ^[17]	
Signal transduction	TGF-β	Fresolimumab	Breast cancer (ORR 0), Phase 2 ^[18]	Selectively or non-selectively neutralizing TGF-β molecules
		NIS793	Solid tumor (OOR 2.5%), Phase 1 ^[19]	
		SAR439359	Solid tumor (OOR 8%), Phase 1 ^[20]	
	TGFβR I	Galunisertib	Rectum cancer (pCR 32%), Phase 2 ^[25] Liver cancer (median OS 18.8 months), Phase 1 ^[21]	Blocking intracellular TGFβRI signaling through small molecule inhibitors
		Vactosertib	Colon rectum cancer (ORR 15.2%), Phase 1 ^[29]	
	TGFβR II	IMC-TR1	Solid tumor, severe adverse events, Phase 1 ^[30]	Blocking the signal transduction of transmembrane TGFβR II using antibodies
Bispecific antibody	PD-L1/	M7824	Solid tumor, limited efficacy, Phase 3 ^[36]	Simultaneously targeting PD-L1 and TGF-β
	TGF-β	SHR-1701	Unresectable NSCLC (pCR 26%), Phase 2 ^[37]	
Cell therapy	TGFβR II	CAR-T	Liver cancer (ORR 50%), Phase 1 ^[40]	Specifically regulating the TGFβ signaling of CAR-T or TCR-T cells
		TCR-T	NCT06218914 (ongoing), Phase 1 ^[42]	

Notes: NSCLC: non-small-cell lung cancer; ORR: objective response rate; pCR: Pathological complete response.

瘤的类型、分期和药物的设计等多方面因素有关，这还需要更多的基础和临床研究去验证。目前靶向TGF-β的细胞治疗策略都是通过TGF-βR II 的负显性修饰来改造T细胞的TGF-β通路，然而，这种策略主要影响的是基因工程改造的T细胞本身的功能，对肿瘤免疫微环境的影响较少。对于能分泌TGF-β抗体的基因工程T细胞而言，其分泌的TGF-β抗体在影响基因工程T细胞本身以外，还能调节免疫微环境，使之更有利于抗肿瘤免疫反应，这可能是另一个值得期待的方向。

利益冲突声明：

所有作者均声明不存在利益冲突。

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