综述

基于肿瘤微环境的CAR-T治疗研究进展

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摘要：嵌合抗原受体T(chimeric antigen receptor T，CAR-T)细胞疗法在治疗血液肿瘤方面已具有显著的疗效，然而CAR-T对实体瘤的治疗仍处于起步阶段。实体瘤的主要特征是细胞增殖和血管形成异常，导致邻近的肿瘤微环境改变。刺激肿瘤微环境会促进实体瘤发展和侵袭性的变化。因此，通过逆转实体肿瘤微环境是突破CAR-T细胞在实体瘤困境的有效方法。本综述主要总结了CAR-T细胞在实体肿瘤微环境中面临的挑战，如免疫检查点、靶向趋化因子受体网络、靶向肿瘤血管系统等，为CAR-T细胞疗法提供临床应用的新策略。

关键词：嵌合抗原受体T细胞；实体肿瘤；肿瘤微环境

Research progress in CAR-T therapy based on tumor microenvironment

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Abstract: Chimeric antigen receptor T (CAR-T) cell therapies have shown remarkable efficacy in the treatment of hematologic tumors, but the treatment of solid tumors with CAR-T is still in its infancy. Solid tumors are characterized by abnormal cell proliferation and angiogenesis, leading to changes in the adjacent tumor microenvironment. Stimulating the tumor microenvironment promotes changes in the development and aggressiveness of solid tumors. Therefore, reversing the solid tumor microenvironment is an effective way to break through the dilemma of CAR-T cells in solid tumors. This review mainly summarizes the challenges faced by CAR-T cells in the solid tumor microenvironment, such as targeting immune checkpoints, targeting chemokine receptor networks, targeting tumor vascular system, etc., and providing new strategies for clinical application of CAR-T cell therapy.

Key Words: chimeric antigen receptor T; solid tumor; tumor microenvironment

在机体处于肿瘤、自身免疫性疾病及过敏等状态时，T细胞作为机体内重要的免疫细胞，通过主要组织相容性复合体物限制性方式识别并靶向杀伤肿瘤细胞[1]。但是体内T细胞对恶性肿瘤的免疫应答功能的有限性，使其不足以满足机体长期战斗状态需求。为克服这一缺陷，研究者尝试通过基因编辑对T细胞进行嵌合抗原受体(chimeric antigen receptor，CAR)修饰来增强T细胞的免疫功能[2]。CAR载体赋予T细胞不依赖主要组织相容性复合体物分子，能够直接识别肿瘤抗原。CAR载

收稿日期：2023-07-11

基金项目：青岛市科技计划园区培育项目(22-3-5-yqpy-21-qy)

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体使T细胞能够识别更广泛的靶抗原，达到靶向性强、杀瘤范围广的目的。

CAR-T细胞疗法已在非霍奇金淋巴瘤、T急性淋巴细胞白血病等血液肿瘤中展开了临床研究并取得了重大进展[3,4]，为晚期血液瘤患者提供了希望。全球已有Kymirah、Yescarta、Tecartus、Breyanzi、Abecma、Relma-cel、Carvykti等7款CAR-T细胞药物获批。可是，CAR-T细胞疗法在实体肿瘤中的研究仍处于初级阶段。一方面，实体瘤细胞抗原的异质性以及特异性肿瘤抗原的缺乏，使CAR-T难以对肿瘤细胞进行精准的靶向性识别和杀伤；另一方面，实体瘤特殊的肿瘤微环境(tumor microenvironment，TME)使CAR-T难以浸润肿瘤组织。本综述总结了CAR-T细胞通过靶向TME，如免疫检查点、细胞外基质、血管系统，来增强CAR-T细胞对实体瘤的疗效，为日后CAR-T在实体瘤中的研究提供理论依据。

1 CAR结构演变

CAR是一个人工合成的重组蛋白，是CAR-T细胞的核心部分。CAR结构主要由胞外抗原识别域、细胞膜上的铰链与跨膜结构域、胞内信号转导区三个部分组成。抗原识别域是可变区重链和轻链组成的单链可变片段(single-chain fragment variable，scFv)，该结构允许T细胞与抗原结合；铰链与跨膜区主要起连接作用，影响scFv活性、促进CAR在T细胞表面的表达；胞内信号转导区负责提供T细胞活化所需的信号[5]。

CAR结构目前已经历了五次改进。第一代的CAR是由Eshha等[6]发明的，由一个特异性的scFv片段和一个分化簇(cluster of differentiation，CD) 3ζ信号域两部分组成。但临床试验证明，第一代CAR-T细胞在体内无法大量增殖，抗肿瘤活性有限，未能广泛应用。第二代和第三代的CAR在CD3ζ信号域上游各增加了1~2个共刺激结构域，如CD28、CD137。与第一代CAR相比，共刺激结构域可增加CAR-T细胞产生细胞因子，并使CAR-T细胞的增殖能力、活化水平显著提高[7,8]。第四代CAR分子是在第二代、第三代CAR的基础上引入了一些细胞因子，如促炎症细胞因子白介素-12和白介素-15，使T细胞被激活的同时释放出更多的细胞因子，改善肿瘤微环境。第五代CAR结构是在第二代的基础上，新增了激活其他信号通路的共刺激结构域，如白介素-2Rβ、信号转导及转录激活蛋白3/5，提供了抗原依赖的细胞因子信号[9](图1)。

2 肿瘤微环境

TME是指肿瘤细胞生存的环境，主要由细胞外基质、免疫细胞、炎症细胞、成纤维细胞等成

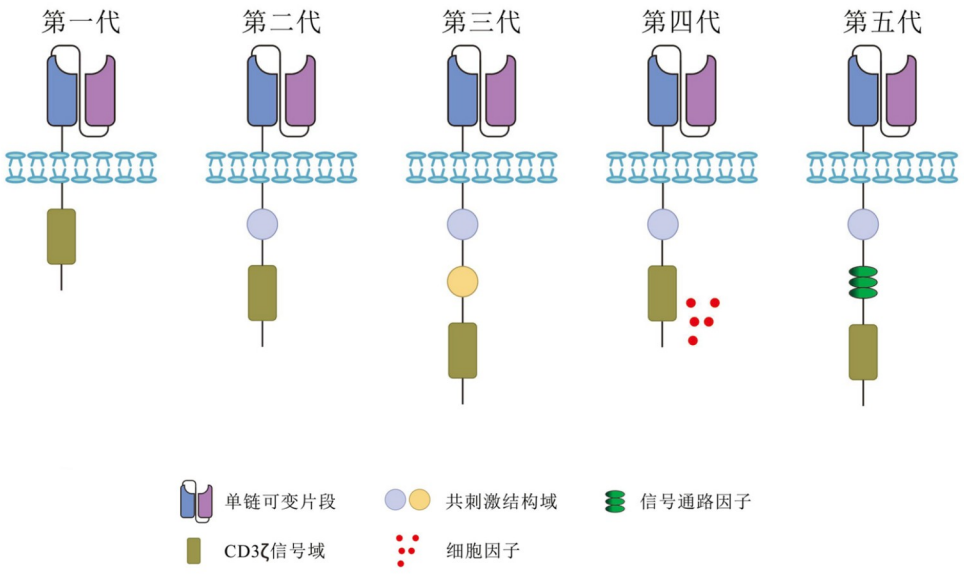


图1 CAR分子的结构和发展

分构成。已有研究表明，TME复杂性与肿瘤生长、转移和对肿瘤的治疗效果有关，同时TME也是影响免疫系统内的细胞在实体肿瘤中浸润及活化的重要因素[10,11]。

细胞外基质细胞和细胞外基质共同构成天然的物理屏障。实体瘤内大量的细胞外基质会导致结缔组织的增生，促进肿瘤细胞的扩散。免疫系统内的细胞如肿瘤相关巨噬细胞经过持续的肿瘤抗原刺激和免疫激活后，会进入耗竭状态，导致免疫抑制微环境的形成[12]。此外，由于肿瘤异常代谢带来的间质液压力升高、pH值低、缺氧等特征也会影响T细胞活性。因此，提高免疫细胞耐受力、激活力或恢复免疫系统固有的肿瘤杀伤效能、重塑积极的肿瘤免疫环境，可对免疫治疗产生综合协同应答效果。

3 CAR-T与实体肿瘤微环境

3.1 针对免疫检查点

免疫检查点是一类免疫抑制性分子，在免疫细胞上表达，调节细胞激活程度，维持机体自身的耐受性，避免过度反应引起的组织损伤。然而，某些抑制性免疫检查点的过度表达，如T细胞内的程序性细胞死亡蛋白-1(programmed cell death protein-1，PD-1)和细胞毒T淋巴细胞相关抗原-4(cytotoxic T lymphocyte antigen-4，CTLA-4)，会使T细胞失去杀伤能力[13,14](图2A)。除此之外，还可通过配体PD-L1与细胞表面抗原CD80结合，CTLA-4与CD80、CD86结合产生抑制T细胞的信号[15,16]。

为提高CAR-T细胞在实体肿瘤中的治疗效果，临床上已开展了定点靶向PD-1、PD-L1和CTLA-4、淋巴细胞活化基因3、细胞死亡受体等免疫检查点的研究[17-21]。在乳腺癌小鼠模型中，通过人表皮生长因子-2疫苗和抗PD-1抗体联合使用会增强CAR-T细胞对乳腺癌的治疗效果，阳性乳腺癌小鼠的存活率得到显著提高[17]。Gargett等[18]在黑色素瘤治疗中采用以GD2为靶点的第三代CAR-T细胞，发现CAR-T细胞可以重复刺激PD-1的表达，增加诱导黑色素瘤细胞死亡的敏感性。GD2靶点、化疗药物和PD-1靶点三者的联合使用会更好促进CAR-T细胞在神经母细胞瘤中的持久性和抗瘤性[19]。在恶性胸膜间皮瘤患者体内，间皮素靶点与PD-1拮抗剂联合使用的CAR-T细胞会整体延长患者6.2个月的寿命[20]。此外，CAR-T与免疫检查点的结合在难治性弥漫性大B细胞淋巴瘤、卵巢癌和成神经细胞瘤等多种肿瘤治疗领域均取得了突破性的进展[21,22]。

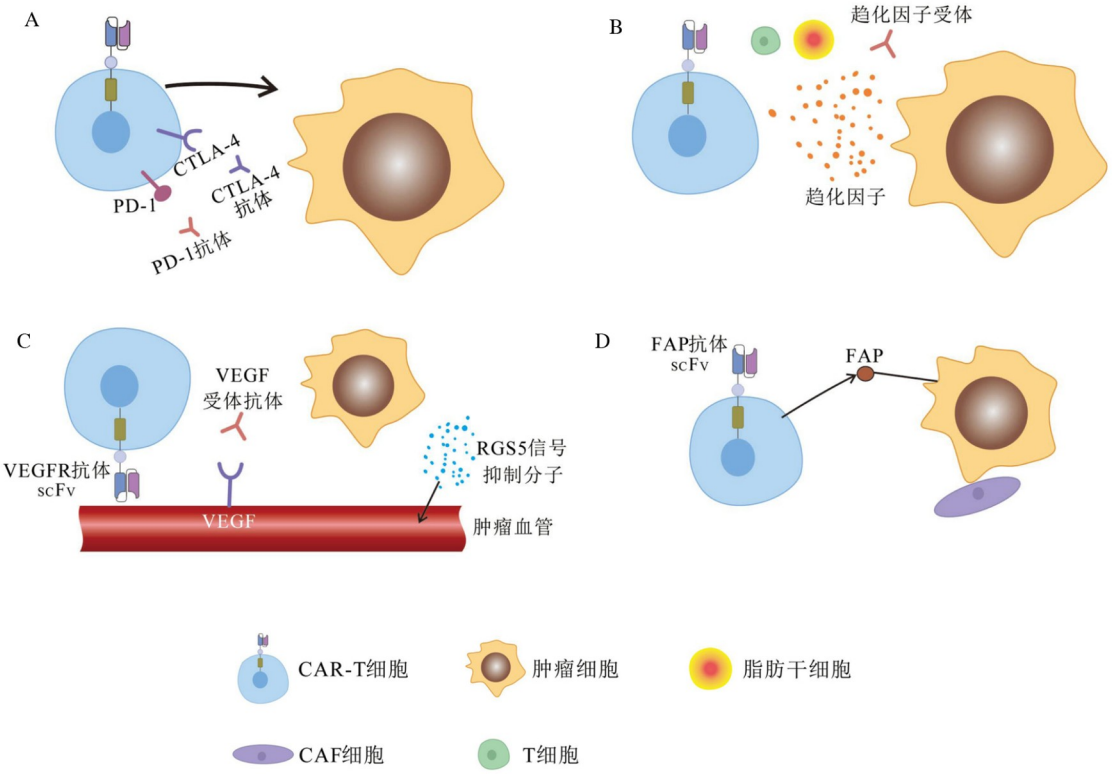
3.2 靶向趋化因子及其受体家族

趋化因子与趋化因子受体(chemokine/chemokine receptor，CXCL/CXCR)的多向结合共同构成复杂的网络系统，成为影响T细胞转运和浸润的重要分子。多种实体瘤实验已经证明，趋化因子通过将效应细胞招募到炎症部位的方式影响肿瘤发生发展。其中，CXCR2/CXCL1-2-5-8及CXCR4/CXCL12的高表达会促肿瘤发生[23-26]。

以靶向CXCL/CXCR网络的方式促进抗肿瘤免疫应答成为一种新型的治疗方案。Peng等[27]和Nagarsheth等[28]证明，CXCR3是招募免疫细胞的关键受体，CXCR3配体CXCL9和CXCL10的缺失会抑制效应T细胞和NK细胞向肿瘤运输。CXCR2配体CXCL8能够刺激CXCR2表达，吸引中性粒细胞和单核细胞髓源性抑制细胞到肿瘤微环境中，促进肿瘤细胞的存活、增殖[29]。在肺腺癌和胰腺癌的治疗中，白介素-7、趋化因子19和CAR-T细胞共表达后小鼠生存率提高到100%[30,31]。此外，CXCL12受体CXCR4拮抗剂(LY2510924)和PD-L1抑制剂(Durvalumab)联合使用对晚期、难治性胰腺癌和直肠癌患者也表现出较好的安全性和耐受性[32]。Grover等[33]构建了定点靶向CD30和趋化因子4受体的CAR-T细胞，新型的CAR-T细胞对霍奇金淋巴瘤和皮肤T细胞性淋巴瘤疾病具有明显的改善效果。Majzner等[34]指出，对H3K27M突变的弥漫性中线胶质瘤患者脑部注射GD2 CAR-T细胞后，患者的血浆和脑脊液中促炎症细胞因子分泌增加。近日，国内生物公司首次将CXCR5与改造的EGFR CAR-T细胞结合，制备成具有高迁移能力的CAR-T细胞，应用于非小细泡肺癌治疗[35](图2B)。

3.3 靶向肿瘤血管系统

实体瘤紊乱的血管系统会阻碍T细胞浸润到肿瘤组织。针对这一情况，临床上会采用血小板衍生生长因子受体(platelet-derived growth factor receptor，PDGFR)信号通路、G蛋白信号通路调节蛋白5(regulator of G protein signaling 5，RGS5)、血



A：针对免疫检查点，CAR-T细胞联合免疫检查点PD-1、PD-L1、CTLA-4阻断剂发挥效用；B：靶向趋化因子及其受体家族，CAR-T细胞中加入趋化因子受体以改善T细胞向肿瘤运输；C：靶向肿瘤血管系统——抗VEGFR CAR-T细胞破坏肿瘤血管、通过VEGF受体抗体抑制肿瘤血管生成或者抑制RGS5信号因子使周细胞和肿瘤血管正常化；D：靶向肿瘤细胞外基质——通过FAP和肿瘤抗原双靶向CAR-T细胞，同时靶向CAF细胞和肿瘤细胞, 降低肿瘤细胞外基质

图2 CAR-T与肿瘤微环境

管内皮生长因子/血管内皮生长因子受体(vascular endothelial growth factor/vascular endothelial growth factor receptor，VEGF/VEGFR)通路方法调控T细胞的浸润[36,37](图2C)。

PDGFR信号通路通过激活多种下游通路，介导横纹肉瘤的发生和发展。人源化的、特异性PDGFR CAR-T细胞会产生大量的白介素-2、肿瘤坏死因子α和干扰素γ，对横纹肌肉瘤表现出有效的治疗效果[36]。在肿瘤新生血管成熟的初期，高表达的RGS5会调节血管周细胞的分化与募集，参与血管成熟的调控。RGS5可降低新生血管对抗VEGF所致的血管退行性疾病的敏感性，未来RGS5将会成为新型的抗血管生成靶点[37]。Buckanovich等[38]通过使用内皮素-β受体抗体BQ-788作用于内皮素-1增强T细胞对实体肿瘤的浸润，促进免疫疗法对实体肿瘤的敏感性。

VEGF/VEGFR信号通路在血管形成过程中有促进内皮细胞的增殖和迁移，增加毛细血管的通透性的作用，在大多数实体瘤组织中呈高水平表达。VEGF阻断剂可使粒细胞-巨噬细胞集落刺激因子表达上调，促进T细胞的增殖，达到肿瘤治疗效果[39]。研究还发现，特异性靶向VEGFR1、VEGFR2的CAR-T细胞能够在不同类型的肿瘤环境中发挥抗肿瘤和血管生成能力[40,41]。因此，RGS5及其信号通路、内皮素β受体、VEGF/VEGFR信号通路有望成为增强CAR-T细胞治疗实体瘤效果的新靶点。

3.4 靶向肿瘤细胞外基质

肿瘤相关成纤维细胞(cancer-associated fibroblasts，CAF)是TME的关键组成成分。在肿瘤细胞的刺激下，CAF通过自分泌和旁分泌途径分泌生长因子β、表皮生长因子、VEGF、CXCL12等因子形成免疫抑制环境，构建物理屏障，限制或困住T细胞，进而阻止T细胞等免疫细胞进入肿瘤，呈现出促进肿瘤生长和维持肿瘤存活的正反馈[42-44]。

因此，靶向CAF为肿瘤治疗提供了新策略。目前，在实体肿瘤中可以通过细胞表面的标记基因去除CAF、促使成纤维细胞恢复静息状态、靶向下游效应分子与CAF的激活信号、靶向CAF产生的细胞外基质蛋白这4种方法实现对CAF的靶向编辑[45]。

成纤维细胞活化蛋白(fibroblast activation protein，FAP)是一种跨膜丝氨酸蛋白酶，在多种类型癌症的原瘤成纤维细胞亚群中广泛表达。FAP选择性高、表达于CAF细胞表面，被视为一个潜在的良好靶点。迄今为止，FAP CAR-T细胞疗法已在间皮瘤、肺癌、乳腺癌、结肠癌和胰腺癌的8项研究中得到了证实[47-49]。FAP CAR-T同时也会伴随不可避免的不良反应发生，在动物实验中，FAP CAR-T会诱导小鼠贫血、体重降低、骨骼发育不全[47]。为解决这一困境，Kakarla等[50]使用不同的scFv序列构建FAP CAR载体，改进后的FAP CAR-T细胞在体外不仅能有效识别和裂解FAP阳性靶细胞，还大大减少了细胞的毒副作用(图2D)。

4 总结及展望

CAR-T细胞疗法被认为是最有前途的癌症治疗方法之一，其在血液系统瘤中的运用已取得了优异的疗效。但在实体瘤治疗方面，复杂的肿瘤微环境成为限制CAR-T细胞疗法的一个主要障碍。因此，重塑肿瘤微环境的细胞成分是打破CAR-T细胞局限的有效方法。基于肿瘤微环境与免疫细胞之间的相互作用关系，CAR-T细胞与免疫检查点阻断剂PD-1、PD-L1和CTLA-4联合使用可以增强CAR-T的杀伤活性，为CAR-T的实体瘤治疗提供了新的思路。除此之外，趋化因子受体网络、肿瘤血管系统、细胞外基质对CAR-T细胞能力的提高也有很大的潜力。本文概述了实体瘤TME对CAR-T细胞疗法的影响，并讨论了通过优化CAR结构和改善TME环境来增强CAR-T细胞功效的方法。相信不久的将来，研究人员会在提高CAR-T疗效的同时避免脱靶效应、细胞因子风暴等副作用发生，提高细胞免疫治疗的安全性，为癌症患者带来福音。

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