DOI:10.3872/j.issn.1007-385x.2025.06.001

·专家论坛·

靶向实体瘤CAR-T细胞设计：安全性与通用性提升策略

邱毓灵,廖天艺,刘宝瑞,李茹恬(南京大学医学院附属鼓楼医院 肿瘤中心,江苏 南京 210008)

李茹恬 教授,博士研究生导师,南京大学医学院附属鼓楼医院肿瘤科执行主任、肿瘤中心主任医师,美国得克萨斯大学MD安德森癌症中心访问学者,获评首批国家优秀青年医师,江苏省杰出青年基金获得者,江苏省“333”工程第二层次人才。主要研究方向为肿瘤的“通用型”治疗性疫苗及细胞治疗。先后创立了“原位疫苗”体系和“通用型”工程化淋巴细胞体系。发表学术论文72篇,其中SCI收录论文36篇,单篇论文发表期刊最高影响因子27.4,H指数31;参编肿瘤学英文专著1部,中文专著4部;作为负责人,先后承担5项国家自然科学基金及多项区域性重点基金项目。相关研究成果(作为主要完成人)获中华医学科技奖三等奖、高等教育国家级教学成果奖二等奖、江苏省科学技术一等奖及二等奖、江苏省医学科技一等奖及二等奖、江苏省医学新技术引进一等奖等。

[摘 要] 嵌合抗原受体基因修饰T细胞(CAR-T细胞)疗法是一种肿瘤免疫治疗方法:来自人体的T细胞在体外经遗传学修饰、表达特异性嵌合抗原受体(CAR),然后将其回输入患者体内,用于靶向识别和消除肿瘤细胞。尽管CAR-T细胞疗法在血液系统肿瘤治疗中取得了较为显著的成功,其在实体瘤治疗中仍面临障碍。细胞因子释放综合征(CRS)等免疫相关不良反应(irAE)制约了CAR-T细胞的安全应用,肿瘤相关抗原(TAA)的异质性限制了单一CAR-T细胞的广谱适用性,也制约了其通用型开发。鉴于此,要使CAR-T细胞疗法在实体瘤临床治疗中得到应用,还需开展进一步的改良与提升研究。本文围绕实体瘤中CAR-T细胞疗法,从“CAR基因修饰策略”、“通用免疫受体的再靶向策略”及“抗原通用性‘赋靶’策略”三个方面对CAR-T细胞领域中为提高安全性和通用性所进行的探索进行述评,系统剖析各策略的研究路径、优势及局限性,并展望未来发展方向。通过综述CAR-T细胞安全性和普适性设计策略的进展,本文旨在为实体瘤的CAR-T细胞疗法研发提供创新思路。

[关键词] 实体瘤免疫治疗;嵌合抗原T细胞疗法;脱靶效应;开关CAR-T细胞
[中图分类号] R730.51 [文献标识码] A [文章编号] 1007-385x(2025) 06-0559-11

Design of CAR-T cells targeting solid tumors: strategies for enhancing safety and universality

QIU Yuling, LIAO Tianyi, LIU Baorui, LI Rutian (The Comprehensive Cancer Center, Nanjing Drum Tower Hospital Affiliated to Nanjing University Medical School, Nanjing 210008, Jiangsu, China)

[Abstract] Chimeric antigen receptor gene-modified T (CAR-T) cell therapy represents an immunotherapeutic approach wherein autologous T cells are genetically engineered *ex vivo* to express specific chimeric antigen receptors (CARs), expanded, and reinfused into patients to specifically recognize and eliminate tumor cells. Despite substantial efficacy in hematological malignancies, CAR-T cell therapy encounters significant barriers in solid tumors. Immune-related adverse events (irAEs), including cytokine release syndrome (CRS), compromise safety profiles, while tumor-associated antigen (TAA) heterogeneity restricts both single-target CAR-T cell applicability and universal CAR-T cell development. Consequently, breakthrough refinements remain essential for clinical translation in solid tumors. This review examines CAR-T cell therapy for solid tumors, critically evaluating safety and universality enhancement strategies through three core approaches: structural CAR design optimization, universal immune receptor retargeting, and antigen universality augmentation. Each approach undergoes systematic analysis of research pathways, advantages, and limitations, with future trajectories delineated. By synthesizing advances in safety and universal design paradigms, the review aims to establish innovative frameworks for CAR-T cell therapeutic development in solid tumor therapeutics.

[Key words] solid tumor immunotherapy; chimeric antigen receptor gene-modified T (CAR-T) cell therapy; off-target effect; switchable CAR-T cell

[Chin J Cancer Biother, 2025, 32(6): 559-569. DOI:10.3872/j.issn.1007-385x.2025.06.001]

[基金项目] 国家自然科学基金(No.82272852);江苏省杰出青年基金(No. BK20240017)
[作者简介] 邱毓灵(1999—),女,博士生,主要从事肿瘤免疫治疗基础与临床的研究
[通信作者] 李茹恬(扫码获取作者联系方式)

过继性细胞疗法(adoptive cell therapy,ACT)通常可被分为3类:基于肿瘤浸润T细胞(tumor-infiltrating lymphocyte,TIL)的ACT、基于T细胞受体(T-cell receptor,TCR)修饰的ACT和基于嵌合抗原受体(chimeric antigen receptor,CAR)修饰的ACT[1-3]。近年来也涌现出了许多新型的细胞治疗如CAR修饰的自然杀伤细胞(CAR-modified natural killer cell,CAR-NK细胞)疗法[4]和CAR修饰的巨噬细胞(CAR-modified macrophage,CAR-M细胞)疗法[5]。在众多工程化细胞治疗中,CAR-T细胞走得最远,美国食品药品监督管理局(Food and Drug Administration,FDA)和/或中国国家药品监督管理局(National Medical Products Administration,NMPA)批准了多种CAR-T细胞治疗血液系统恶性肿瘤的产品[6]。在CAR-T细胞实体瘤领域也有众多的临床试验正在开展[7-14],然而,CAR-T细胞的实体瘤治疗仍然有无法忽略的阻碍[15]。

最为关键的障碍是免疫相关不良反应(immune-related adverse reaction,irAE)的发生[16]。CAR-T细胞疗法引起的irAE主要包括严重的细胞因子释放综合征(cytokine release syndrome,CRS)、免疫效应细胞相关神经毒性综合征(immune effector cell-associated neurotoxicity syndrome,ICANS)和脱靶效应[17]。其中,脱靶效应是实体瘤CAR-T细胞治疗中特有的问题,在多种CAR-T细胞的实体瘤治疗中均有发生[18-20]。当下实体瘤中常用的CAR-T细胞靶点均在正常组织中有不同程度的表达,这是导致脱靶效应的最重要原因[21]。一个典型的案例是,1例接受HER2靶向CAR-T细胞治疗的患者在治疗后因脱靶效应而呼吸窘迫致死[22]。此外,通用性也是CAR-T细胞实体瘤应用的一大挑战。最初,设计CAR-T细胞的目的是对T细胞进行遗传修饰,使其表现出不受主要组织相容性复合体(major histocompatibility complex,MHC)限制的特异性[23-24],因此理论上具有通用性。然而,实体瘤CAR-T细胞的靶点多为肿瘤相关抗原(tumor-associated antigen,TAA),不同实体瘤通常具有不同的TAA表达谱[25],这使靶向特定某种TAA的CAR-T细胞在实体瘤中的应用较为局限;另一方面,抗原逃逸通过介导靶点丢失[26-28],使单一靶向CAR-T细胞的持久性应答中断,引发获得性耐药。最后,实体瘤微环境(tumor microenvironment,TME)较血液系统肿瘤更为复杂,对CAR-T细胞疗法的有效性造成了一定的负面影响[15, 29-30]。TME中肿瘤相关成纤维细胞(tumor-associated fibroblast, TAF)和细胞外基质(extracellular matrix,ECM)的存在以及其他如缺氧、低pH、免疫抑制性细胞的浸润等因素也会抑制CAR-T细胞的功能[31]。更重要的是,肿瘤抗原的长期刺激会降低CAR-T细胞增殖能力,进一步导致其功能降低和耗竭[32]。

目前,已有多种TME重塑策略,如免疫检查点抑制剂(immune checkpoint inhibitor,ICI)[33-34]和针对ECM的策略[35-36],本文把目光聚焦于提高CAR-T细胞的安全性和普适性。文章从“开关”设计、再靶向设计和抗原通用化设计(“赋靶”)三方面阐述近年来在提高CAR-T细胞治疗实体肿瘤的安全性和/或通用性方面所做的努力。

1　基于CAR基因修饰的开关策略

通过基因修饰CAR可实现对CAR-T细胞功能“开启”和“关闭”状态的精确调节,显著增强CAR-T细胞的靶向能力,提高安全性。此外,某些精妙的设计还提高了疗法的通用性。

1.1　“开”:启动CAR-T细胞的策略

1.1.1　IF-Then:条件启动的CAR

条件启动的CAR为CAR基因的表达设置了一个“条件性调控开关”,需要特定的生物因素或理化因素刺激诱导CAR基因表达并与靶点结合,发挥CAR-T细胞的杀伤作用。理化刺激因素包括利用核易位启动子结合的光感系统(light-inducible nuclear translocation and dimerization,LINTAD)[37]、利用T细胞自然表达的超声敏感型Piezo1离子通道的ReCoM系统[38]、利用热激蛋白(heat-shock protein,HSP)启动子的热敏开关[39]和基于缺氧诱导因子1α(HIF-1α)这一转录因子设计的缺氧开关[40-41]。

在条件启动的CAR中,基于合成Notch受体SynNotch的逻辑门控策略因其创新性设计备受关注[42],目前已经迭代三代,在提高安全性的同时也将通用性纳入考量。第一代SynNotch设计为当SynNotch结合与之对应的第一抗原后,T细胞才表达能够结合第二抗原的CAR[43]。这样的策略采用双抗原串联激活机制,相当于“AND逻辑门控”,只有两种抗原均表达的时候CAR-T细胞才会发挥功能,提高了安全性。SynNotch的第二代引入了负选择机制,基于亲和力梯度筛选进一步提高安全性。研究者设计了可表达低亲和力SynNotch受体和高亲和力CAR的CAR-T细胞。由于肿瘤细胞的抗原密度更高,低亲和力SynNotch受体可充当过滤器,仅在接触具有高抗原表达的靶细胞时被激活并启动CAR的表达。一旦通过这个初始过滤器,诱导出高亲和力CAR的T细胞就可以进行强效的杀伤[44]。合成膜内蛋白水解受体(synthetic intramembrane proteolysis receptor,SNIPR)-CAR是第三代基于SynNotch受体

设计的CAR-T细胞,其模块化的设计在提升安全性之余增强了CAR的通用性[45],具有更佳的临床转化潜力。SNIPR被拆分为包括细胞外结构域(extracellular domains,ECD)、跨膜结构域(transmembrane domain,TMD)、细胞内近端膜域(intracellular proximal membrane domain,IMD)和转录因子(transcription factor,TF)在内的多个模块。这些基于合成生物学的顶端设计模块共同构成了CAR的"模块化架构"体系,可以根据不同的需求进行灵活组装,对于CAR-T细胞的设计及调控具有重要意义。近年有报道将其与超声调控结合,以达到对于CAR的无创精准调控[46]。与SynNotch类似的还有由人类SH3结构域支架设计的Sherpabodies,同样具有模块化和多功能性特征,可作为提高CAR-T细胞安全性的平台[47]。

1.1.2 CAR的功能性组装策略

CAR的功能性组装主要是通过工程化设计,将CAR分子拆分为两个部分,仅在特定因素存在时组装为具有完整结构和功能的CAR。介导此过程的是各种二聚化剂,如雷帕霉素[48]及其衍生物AP21967[49-51]或AP1903[52]、来那度胺[53]等;也有基于蓝光刺激的组装方案(如LiCAR)[54]。

这一策略最早是WU等[49]于2015年提出,他们设计的CAR由两部分组成:一部分包含细胞外抗原结合结构域(scFv)、CD8铰链和跨膜结构域、4-1BB共刺激基序和异二聚化结构域FKBP(FK506 binding protein);第二部分由DAP10胞外结构域和CD8跨膜结构域、4-1BB共刺激基序、异二聚化结构域FRB*(T2089L mutant of FKBP-rapamycin binding domain)和CD3-zeta信号链组成。FKBP和FRB*模块的二聚化可被雷帕霉素及其衍生物AP21967介导,从而控制CAR的功能。最近,出于进一步提高安全性的考虑,雷帕霉素的酶靶向递送系统被纳入此策略以治疗表达HER2的实体瘤[55]。由于明胶酶靶向的纳米粒子仅在肿瘤部位释放开关分子且具有缓释作用,因此具备双重优势:在不影响疗效的同时提高安全性,并通过缓释作用延缓T细胞的耗竭。

另一个值得注意的概念是实现掩蔽的CAR-T细胞[56],不过相关研究较少。掩蔽肽通过蛋白酶可识别序列连接到CAR-T细胞的胞外段,遮蔽CAR结构中的抗原结合位点。当CAR-T细胞浸润到TME时,TME中丰富的蛋白酶将催化这些掩蔽肽水解,使CAR-T细胞解除被掩蔽状态并恢复靶向杀伤功能。

上述策略的主要优势在于对CAR-T细胞活性启动的条件性调节,但它们也有一定的缺点:相对复杂的CAR结构设计提高了转染难度,制约技术的普适性与转化效率。

1.2 "关":抑制CAR-T细胞的策略

"关"策略主要通过诱导CAR-T细胞凋亡或抑制其细胞活性来预防不良反应的发生。目前此类策略包括自杀基因、CAR的蛋白酶水解、CAR拆解和抑制性CAR等。

1.2.1 诱导CAR-T细胞凋亡/耗竭的设计

这些策略通过诱导细胞凋亡或耗竭,实现对活化CAR-T细胞的全面控制,代表了实现"关闭"CAR-T细胞的最彻底"关闭"机制,可根据机制大致分为凋亡诱导和靶向清除两类。凋亡诱导主要涉及自杀基因的表达或抗体依赖性细胞介导的细胞毒性(antibody-dependent cell-mediated cytotoxicity,ADCC),靶向清除则通过特异性抗体阻断CAR信号通路来实现。尽管这些策略仅在以CD19为靶点的CAR-T细胞治疗血液系统恶性肿瘤中得到了验证,它们也具有应用于实体瘤CAR-T细胞疗法的潜力。

常用自杀基因/蛋白包括单纯疱疹病毒-胸苷激酶(herpes simplex virus-thymidine kinase,HSV-TK)[57]、诱导型半胱天冬酶9(inducible cysteine 9,iC9)[58-61]和Fas相关死亡结构域蛋白(FADD)[62]。其中,研究最多也是最灵活的是iC9相关的设计,可与雷帕霉素类似物Rimiducid/AP1903构成生物正交开关,进一步提高安全性[63]。该策略也已经过临床的验证,是自杀基因策略中最为成熟的一种,具有很强的临床转化潜力。自杀受体主要是利用已获批临床应用的抗体介导ADCC作用以杀死靶细胞,如利妥昔单抗[64]/西妥昔单抗[65]。

靶向耗竭策略主要是利用酪氨酸激酶抑制剂达沙替尼[66-68]对下游信号通路的抑制作用。通常,CAR与靶分子结合后的信号传导涉及SRC家族激酶淋巴细胞特异性蛋白酪氨酸激酶(lymphocyte specific protein tyrosine kinase,LCK)的自磷酸化[69],而达沙替尼可阻断LCK的三磷酸腺苷(ATP)结合位点,从而可逆性地"关闭"CAR-T细胞功能。由于该通路在CAR-T细胞中高度保守,所以达沙替尼作为安全开关也具有一定的通用性。

1.2.2 CAR的功能性蛋白酶水解

还有一类方法是通过一些可调控的因素控制嵌合抗原受体的水解,主要采用两类分子工具[蛋白酶抑制剂阿叔那匹韦(asunaprevir,ASV)和蛋白水解靶向嵌合体(protein hydrolysis-targeted chimeras,PROTAC)]进行设计,如SWIFF-CAR[70]和CASH-IT[71]。在SWIFF-CAR中,CAR的末端连接丙型肝炎病毒NS3蛋白酶(hepatitis C virus NS3 protease,HCV-NS3)及蛋白酶体位点,在无ASV存在时,CAR末端的HCV-N53将发生自剪切从而使CAR在T细胞表面成功表达。而ASV存在时,末端的HCV-N53

无法被裂解,CAR滞留细胞内而不能表达于细胞表面,从而丧失功能。CASH-IT的设计也使用的类似的思路,研究团队合成了一种抑制CAR功能的融合蛋白,在无ASV时此融合蛋白稳定存在并抑制CAR-T细胞功能,而加入ASV后,融合蛋白可被靶向裂解从而解除CAR功能抑制。

PROTAC能够利用泛素-蛋白酶体系统将靶蛋白特异性水解[72-73]。应用于CAR-T细胞领域的PROTAC技术旨在增强CAR-T细胞的抗肿瘤活性[74-75],在提升安全性方面同样具有重要作用。JAN等[53]在CAR的胞内段添加溴结构域,并设计了靶向溴结构域的PROTAC,使CAR能够被靶向降解。LEE等[76]则在胞内段添加了来那杜胺依赖性锌指降解标签,在加入来那度胺后可引发CRL4CRBN-介导的泛素化和蛋白水解。

1.2.3　小分子介导的CAR解构

前面章节介绍了促二聚化剂能够诱导功能性CAR组装,本节将介绍基于抑制二聚化药物设计的CAR-T细胞,包括STOP-CAR[77]和Tet-CAR[78]。它们能够通过阻止胞内分裂的结合域二聚化来破坏CAR信号复合体的形成与功能。其中,STOP-CAR主要依赖计算机模拟设计,而Tet-CAR则是基于“关闭分子”米诺环素与四环素抑制蛋白(TetRB)的高亲和力结合。

1.2.4　抑制性CAR

抑制性CAR(inhibitor CAR, iCAR)是一种创新性的设计策略[79-81]。其核心原理为筛选出正常组织特异性抗原对应的单链可变片段(scFv),将其通过跨膜区域与免疫抑制受体(CTLA-4和PD-1)的信号结构域相连,可在识别正常组织抗原时触发抑制性信号通路,特异性抑制T细胞活性[79]。当CAR-T细胞识别到正常组织抗原,其活性即通过免疫抑制信号通路被抑制,从而提高了安全性。这种思路的核心挑战在于,很难找出一个理想化的、严格满足“正常组织表达且肿瘤不表达”的抗原。此外,iCAR的抑制效率较低,仅能够部分抑制而非完全抑制。BANGAYAN等[82]将其他抑制结构域如LAIR-1或SIGLEC-9纳入PD-1结构域,构建具有双重抑制结构域的iCAR以增强抑制效果。但他们的设计并未达到预期的效果,抑制性CAR的思路需要后期更多的研究完善。

2　基于通用免疫受体的再靶向策略

利用通用免疫受体(universal immune receptor, UIR)构建CAR-T细胞系统,即适配器CAR-T细胞,是一种兼顾安全性和通用性的策略。在这种设计中,CAR-T细胞并不直接靶向肿瘤表面的抗原,而是通过一个类似于“转换插头”的适配器分子完成靶向过程。适配器分子具有两端,一端为靶向端,一端为CAR结合端。靶向端能够与肿瘤表面抗原特异性结合,而CAR结合端可被CAR特异性识别并激活CAR-T细胞。这个策略是整合安全性与通用性的双功能策略,即CAR的结构是固定的,可以通过改变适配器分子的靶向端来靶向不同的肿瘤,而CAR与CAR结合端也可以通过工程化设计来避免体内脱靶。这样的适配器主要分为三类,一类基于抗体-配体结合的适配器接头设计,一类基于蛋白质相互作用或点击化学的接头设计,还有一类利用抗体依赖的细胞毒性策略进行设计,下文将系统阐述各类设计及其原理。

2.1　抗体-配体偶联策略

这种策略是最早发展的设计,主要的设计思路是在靶向肿瘤细胞表面抗原的抗体(monoclonal antibody, mAb)末端再连接上一个标记蛋白(tagged protein, Tag),而将CAR-T细胞的scFv段设计为靶向Tag的scFv(Anti-Tag)。其中,较早出现且研究较为丰富的是抗异硫氰酸荧光素(anti-isothiocyanate fluorescein, Anti-FITC)CAR与FITC-mAb[83-87],在实体瘤如乳腺癌[88]和非小细胞肺癌[85]中也展现出了不逊于常规CAR-T细胞的疗效,并在动物实验中被证明可用于治疗神经内分泌肿瘤[89]。另外,研究[85, 90]表明,FITC-mAb可以剂量依赖性方式调控CAR-T细胞的活性与功能,从而使CRS症状保持在可控制的范围内。近年来,也有研究[91-92]将光开关与Anti-FITC CAR的设计进行结合,进一步提高其可调控性。其他应用于此策略的Tag包括来自酵母转录因子GCN4的肽新表位PNE[93-94]和源自核抗原La-SS-B的短非免疫原性肽基序[95-96],其中,基于PNE设计的开关CAR-T细胞在转移性导管胰腺癌患者的治疗上展现显著临床获益[97]。

另一种设计是利用双特异性T细胞接合器或双特异性抗体(bi-specific T cell engager, BiTE/bispecific antibody, BsAb)充当适配器,BiTE可以特异性地与CAR-T细胞接合,并靶向肿瘤表面抗原[98]。第一个BiTE-CAR-T细胞是将自身蛋白叶酸受体α(folate receptor α, FRα)的胞外结构域与胞内的CAR-T细胞信号转导结构域基因融合,其适配器BiTE分别靶向FRα(CAR-T细胞结合端)和CD20(靶向端),以治疗$CD20^+$的肿瘤[99]。另一团队则利用CD19-CD20 scFv融合蛋白扩展了靶向CD19的CAR-T细胞产品的使用可能[100],提高了目前研究最多、产品最丰富的antiCD19-CAR-T细胞的通用性。还有团队将适配器BiTE基因转入CAR-T细胞内,由CAR-T细胞自分泌CD3 scFv-EGFR scFv融合蛋白[101],这种设计在扩大CD19-CAR-T细胞的“抗原识别谱”的同时,也可吸

引“旁观者”T细胞至肿瘤细胞附近。

2.2 蛋白质相互作用或点击化学策略

除了利用常规抗原-抗体相互作用,适配器设计还有许多新策略。例如,基于蛋白质相互作用的传统的生物素-链霉亲和素配对也在此领域有所应用[102-104]。优化后的生物素接头可激活胰腺肿瘤微环境中的T细胞并识别检测可溶性TGF-β[105]。

同时,也有许多来源于细菌蛋白的适配器系统被开发,如SpyTag/SpyCatcher系统[106-108]与Bs-Bn系统[109]。SpyTag和SpyCatcher两个部分由化脓性链球菌CnaB2蛋白拆分而来,两者可通过酰胺键连接[110]。Barnase是一种核糖核酸酶,Barstar是其特异性抑制剂[111-112]。这两类基于细菌蛋白的系统优势在于,这些蛋白或肽段为细菌独有、特异性高,同时适配器可以直接基于细菌的系统进行生产和表达、性价比高。

催化抗体38C2的应用也值得关注。在生理条件下,38C2独特的活性赖氨酸残基可与1,3-二酮半抗原形成可逆共价键(胺酮)[113],因此,有团队将CAR-T细胞抗原识别段设计为38C2,而其适配器为连接了靶向端的半抗原,通过催化共价键的形成交联CAR-T细胞与肿瘤细胞,在前列腺癌细胞实验中取得良好的效果[114]。

还有一些其他的小分子偶联系统被创新性地引入通用型CAR-T细胞的设计,在提高安全性和通用性之余,拓展了功能性。如,利用亮氨酸拉链设计的SUPRA CAR[115]和基于生物正交修饰的SNAP CAR/synNotch系统[116]。在SUPRA CAR系统中,研究者们还增加了抑制性的通路,在保持通用性的同时增强安全性,展现出多功能的优势[117]。SNAP CAR/synNotch系统中因为引入了synNotch受体,增加了与前述的“IF-Then”策略联合使用的可能性,丰富了CAR-T细胞的功能。

2.3 ADCC策略

ADCC作用是NK细胞杀伤肿瘤细胞的主要机制,人IgG1抗体的可结晶区域(Fc)可与NK细胞上的CD16A受体结合,从而激活NK细胞并引发杀伤作用[118]。基于ADCC作用原理,CLEMENCEAU等[119]设计出了表达Fc受体的T细胞,可通过ADCC作用靶向杀伤B淋巴母细胞样细胞。KUDO等[120]后续改进了信号转导结构域,利用曲妥珠单抗、抗GD2抗体作为适配器,成功介导了T细胞对乳腺癌、胃癌、神经母细胞瘤和骨肉瘤细胞的杀伤。近年来,也有中国学者研究此类CAR-T细胞,将不同种类的FcγR(即CD16A、CD32A和CD64)设计为CAR-T细胞的靶向段,同时与单抗联用,在动物模型中展现出了持续且显著的细胞毒性,通用性强[121-122]。

ADCC策略在通用性上表现优秀,但在安全性上存在不足。其优势在于无需额外设计适配器和CAR结构,仅需根据靶点选择相应商品化抗体即可,操作简便。然而,由于该策略使用的受体(FcγR)在正常人体内天然存在,缺乏足够的肿瘤靶向特异性,导致其安全性欠佳。

传统通用免疫受体策略的主要挑战是抗原性和免疫原性。FITC-mAb会导致体内FITC抗体的产生[84],而正常人血清中存在的亲和素抗体也是基于生物素-链霉亲和素系统应用的壁垒[123]。来源于细菌组分的SpyTag/SpyCatcher系统[106-107]与Bs-Bn系统[109]也可能引发免疫反应。因此,开发具有高特异性且免疫原性弱的适配器,将是未来适用于临床转化的关键研究方向。

3 基于抗原通用性的策略设计

抗原的通用性同样是实现通用型CAR-T细胞的关键因素之一,CD19特异性的CAR-T细胞在血液系统治疗中的成功证明了靶点选择的重要性。为了提升实体瘤靶点的通用性,主要策略包括对肿瘤细胞进行工程化改造以表达特定抗原,以及从实体瘤特异性TME中筛选合适的抗原靶标。

3.1 肿瘤细胞的直接赋靶

赋靶策略作为一种兼具通用性和安全性的策略,在实体瘤CAR-T细胞治疗领域展现出显著优势。该策略的核心是通过特定技术手段将靶抗原直接递送到肿瘤细胞表面或TME。其优势在于能够克服实体瘤TAA的异质性,且可通过选择正常人体不表达的蛋白作为靶抗原来提高特异性,进一步降低脱靶的可能。肿瘤细胞的直接赋靶主要是依靠病毒或其他递送系统来达成。鉴于目前上市的CAR-T细胞产品多为CD19-CAR-T细胞,若能向实体瘤靶向递送CD19抗原,则可直接使用CD19-CAR-T细胞治疗,具有临床转化价值和通用性意义。

溶瘤病毒的安全性和有效性已经在临床试验中得到证明,FDA于2015年批准其临床应用。溶瘤病毒的优势在于可选择性地感染和/或在恶性细胞中复制[124],减少脱靶效应;同时,它具有选择性感染、裂解细胞并募集内源性抗病毒免疫应答的能力[125],能够增强机体对免疫治疗的响应性。研究者们看中了此优势,选取溶瘤病毒向黑色素瘤[127]或三阴乳腺癌[128]递送CD19抗原,在动物模型中延缓了肿瘤生长并提高了中位生存期。另有研究[129]利用溶瘤病毒同时向肿瘤局部递送CD19和BCMA抗原,为联合治疗提供了可能。

利用纳米递送系统是实现肿瘤细胞膜表面修饰抗原的另一重要手段。SUN等[130]开发出的TRUE-CAR-T细胞利用负载融合抗原的DSPE-PEG纳米颗粒作为原位抗原修饰平台，可以剂量依赖性的方式介导CAR-T细胞激活，兼具靶向性和特异性。此外，具有膜插入性的PEG-脂质偶联物也可用于进行肿瘤表面的修饰，ZHANG等[131]设计、合成了可以插入肿瘤细胞膜内的amph-FITC，在小鼠黑色素瘤模型中验证其能够引起CAR-T细胞特异性靶向FITC的杀伤效应。

基于代谢的肿瘤细胞膜重塑也是一种新颖的思路。FAN等[132]基于长链脂肪酸(long chain fatty acid, LCFA)开发出了一种针对肿瘤细胞的抗原修饰策略。肿瘤细胞的脂质代谢异常，更倾向于摄取LCFA，故基于LCFA的递送系统提供了人工抗体插入的可能。在此策略中，研究者也选取FITC作为人工配体，合成不饱和棕榈酸(palmitic acid, PA)结合的Lip-FITC，并证实回输FITC特异性CAR-T细胞后，可在黑色素瘤小鼠模型中观察到显著的治疗效果。

3.2　肿瘤免疫微环境的靶向策略

鉴于实体瘤免疫微环境具有与血液系统肿瘤不同的特点，如具有血液系统肿瘤所不具备的物理屏障，许多研究聚焦于肿瘤细胞外基质中的成分。

成纤维细胞活化蛋白(fibroblast activation protein, FAP)是一种在成纤维细胞(CAF)表面表达的跨膜蛋白，在大多数的上皮来源的恶性肿瘤中呈高表达[133]。FAP靶向的CAR-T细胞[134]在体内和体外均展现出明确的抗肿瘤活性[35]，且有效介导肿瘤结缔组织破坏与降解[135]。

还有科学家将工程化益生菌、通用免疫受体和微环境靶向策略创新性结合，开发出ProCAR平台[136]。其中，适配器分子的靶向端被设计为为胎盘生长因子(PIGF123-144)，可广泛锚定在胶原蛋白、纤连蛋白和硫酸乙酰肝素蛋白聚糖上。这些蛋白聚糖在大多数实体瘤上和肿瘤ECM中含量很高其识别端为超级折叠绿色荧光蛋白(GFP)，可与CAR端的抗GFP纳米抗体结合。该设计的创新点在于利用工程化细菌在低氧/坏死TME中优先定植的特性，使其原位表达并释放适配器分子。这些细菌不仅具有肿瘤靶向性，其本身作为免疫原还可刺激机体免疫反应；同时，其携带的同步裂解电路可在细菌达到一定密度时触发自我裂解，增强了系统的安全性。

也有研究者[137]将上述靶向TME策略与前述的“IF-then策略”进行联合，将synNotch受体设计为识别肿瘤ECM成分，当其被激活后，可诱导CAR-T细胞分泌肿瘤特异性酶——基质金属蛋白酶，从而降解ECM，增加CAR-T细胞的浸润，从而进一步促进CAR-T细胞的激活、扩增与持久活性。

4　结　语

本文综述了提升CAR-T细胞在实体瘤治疗中通用性和安全性的关键策略，梳理当前相关研究的前沿思路，旨在为突破实体瘤CAR-T疗法的瓶颈提供新的视角与启发。未来可从以下几个方面进一步改良：(1)策略整合与联合应用，本文所述策略虽看似相互独立，实则具备协同潜力(部分研究已初步印证)，因此，开发多机制协同、多策略联用的综合方案将是重要发展方向；(2)简化工艺与降低成本，现有部分改造策略流程复杂、成本高昂，限制了临床转化，因此，开发简便、经济且易于规模化生产的策略是推动临床应用普及的迫切需求；(3)平衡安全性与疗效，在严格保障安全性的前提下，需同等重视并优化CAR-T细胞在实体瘤微环境中的浸润能力、持久扩增潜能及强效杀伤活性，避免因过度保守影响疗效；(4)融合人工智能技术，随着人工智能领域的飞速发展，利用机器学习模型预测和优化实体瘤靶点选择及CAR-T设计，有望显著提升治疗精准性与效率。

利益冲突公开声明

所有作者均不存在实际的或潜在的利益冲突。

[参 考 文 献]

[1] JUNE C H, RIDDELL S R, SCHUMACHER T N. Adoptive cellular therapy: a race to the finish line[J/OL]. Sci Transl Med, 2015, 7 (280): 280ps7[2025-02-10]. https://pubmed. ncbi. nlm. nih. gov/25810311/. DOI: 10.1126/scitranslmed.aaa3643.

[2] ROHAAN M W, WILGENHOF S, HAANEN J B A G. Adoptive cellular therapies: the current landscape[J]. Virchows Arch, 2019, 474(4): 449-461. DOI: 10.1007/s00428-018-2484-0.

[3] ZHANG M Y, LIU C J, TU J, *et al*. Advances in cancer immunotherapy: historical perspectives, current developments, and future directions[J/OL]. Mol Cancer, 2025, 24(1): 136[2025-02-10]. https://pubmed.ncbi.nlm.nih.gov/40336045/. DOI: 10.1186/s12943-025-02305-x.

[4] BALKHI S, ZUCCOLOTTO G, DI SPIRITO A, *et al*. CAR-NK cell therapy: promise and challenges in solid tumors[J/OL]. Front Immunol, 2025, 16: 1574742[2025-02-10]. https://pubmed. ncbi. nlm.nih.gov/40260240/. DOI: 10.3389/fimmu.2025.1574742.

[5] LEE C, KWAK C, CHOI M, *et al*. Advancing immunotherapy with innovations in CAR-M engineering for cancer treatment[J/OL]. Int Immunopharmacol, 2025, 156: 114720[2025-02-10]. https://pubmed.ncbi.nlm.nih.gov/40288149/. DOI: 10.1016/j.intimp.2025.114720.

[6] LU J R, JIANG G. The journey of CAR-T therapy in hematological malignancies[J/OL]. Mol Cancer, 2022, 21(1): 194[2025-02-10]. https://pubmed.ncbi.nlm.nih.gov/36209106/. DOI: 10.1186/s12943-022-01663-0.

[7] MAHER J, DAVIES D M. CAR based immunotherapy of solid tumours-a clinically based review of target antigens[J/OL]. Biology

(Basel), 2023, 12(2): 287[2025-02-10]. https://pubmed.ncbi.nlm.nih.gov/36829563/. DOI: 10.3390/biology12020287.

[8] BROWN C E, ALIZADEH D, STARR R, *et al*. Regression of glioblastoma after chimeric antigen receptor T-cell therapy[J]. N Engl J Med, 2016, 375(26): 2561-2569. DOI: 10.1056/NEJMoa1610497.

[9] LOUIS C U, SAVOLDO B, DOTTI G, *et al*. Antitumor activity and long-term fate of chimeric antigen receptor-positive T cells in patients with neuroblastoma[J]. Blood, 2011, 118(23): 6050-6056. DOI: 10.1182/blood-2011-05-354449.

[10] ADUSUMILLI P S, ZAUDERER M G, RIVIÈRE I, *et al*. A phase Ⅰ trial of regional mesothelin-targeted CAR T-cell therapy in patients with malignant pleural disease, in combination with the anti-PD-1 agent pembrolizumab[J]. Cancer Discov, 2021, 11(11): 2748-2763. DOI: 10.1158/2159-8290.CD-21-0407.

[11] AHMED N, BRAWLEY V S, HEGDE M, *et al*. Human epidermal growth factor receptor 2 (HER2)-specific chimeric antigen receptor-modified T cells for the immunotherapy of HER2-positive sarcoma [J]. J Clin Oncol, 2015, 33(15): 1688-1696. DOI: 10.1200/JCO.2014.58.0225.

[12] VITANZA N A, RONSLEY R, CHOE M, *et al*. Intracerebroventricular B7-H3-targeting CAR T cells for diffuse intrinsic pontine glioma: a phase 1 trial[J]. Nat Med, 2025, 31(3): 861-868. DOI: 10.1038/s41591-024-03451-3.

[13] STEFFIN D, GHATWAI N, MONTALBANO A, *et al*. Interleukin-15-armoured GPC3 CAR T cells for patients with solid cancers[J]. Nature, 2025, 637(8047): 940-946. DOI: 10.1038/s41586-024-08261-8.

[14] CHEN N F, PU C F, ZHAO L L, *et al*. Chimeric antigen receptor T cells targeting CD19 and GCC in metastatic colorectal cancer: a nonrandomized clinical trial[J]. JAMA Oncol, 2024, 10(11): 1532-1536. DOI: 10.1001/jamaoncol.2024.3891.

[15] BOCCALATTE F, MINA R, AROLDI A, *et al*. Advances and hurdles in CAR T cell immune therapy for solid tumors[J/OL]. Cancers (Basel), 2022, 14(20): 5108[2025-02-10]. https://pubmed.ncbi.nlm.nih.gov/36291891/. DOI: 10.3390/cancers14205108.

[16] DONG J Y, WU J X, JIN Y, *et al*. In-depth analysis of the safety of CAR-T cell therapy for solid tumors[J/OL]. Front Immunol, 2025, 16: 1548979[2025-02-10]. https://pubmed. ncbi. nlm. nih. gov/40066440/. DOI: 10.3389/fimmu.2025.1548979.

[17] JUNE C H, O'CONNOR R S, KAWALEKAR O U, *et al*. CAR T cell immunotherapy for human cancer[J]. Science, 2018, 359 (6382): 1361-1365. DOI: 10.1126/science.aar6711.

[18] GROSS G, ESHHAR Z. Therapeutic potential of T cell chimeric antigen receptors (CARs) in cancer treatment: counteracting off-tumor toxicities for safe CAR T cell therapy[J]. Annu Rev Pharmacol Toxicol, 2016, 56: 59-83. DOI: 10.1146/annurev-pharmtox-010814-124844.

[19] MAJZNER R G, MACKALL C L. Clinical lessons learned from the first leg of the CAR T cell journey[J]. Nat Med, 2019, 25(9): 1341-1355. DOI: 10.1038/s41591-019-0564-6.

[20] SCHMIDTS A, WEHRLI M, MAUS M V. Toward better understanding and management of CAR-T cell-associated toxicity [J]. Annu Rev Med, 2021, 72: 365-382. DOI: 10.1146/annurev-med-061119-015600.

[21] FLUGEL C L, MAJZNER R G, KRENCIUTE G, *et al*. Overcoming on-target, off-tumour toxicity of CAR T cell therapy for solid tumours[J]. Nat Rev Clin Oncol, 2023, 20(1): 49-62. DOI: 10.1038/s41571-022-00704-3.

[22] MORGAN R A, YANG J C, KITANO M, *et al.* Case report of a serious adverse event following the administration of T cells transduced with a chimeric antigen receptor recognizing ERBB2[J]. Mol Ther, 2010, 18(4): 843-851. DOI: 10.1038/mt.2010.24.

[23] GROSS G, WAKS T, ESHHAR Z. Expression of immunoglobulin-T-cell receptor chimeric molecules as functional receptors with antibody-type specificity[J]. Proc Natl Acad Sci USA, 1989, 86 (24): 10024-10028. DOI: 10.1073/pnas.86.24.10024.

[24] KUWANA Y, ASAKURA Y, UTSUNOMIYA N, *et al*. Expression of chimeric receptor composed of immunoglobulin-derived V regions and T-cell receptor-derived C regions[J]. Biochem Biophys Res Commun, 1987, 149(3): 960-968. DOI: 10.1016/0006-291x(87)90502-x.

[25] MORELLO A, SADELAIN M, ADUSUMILLI P S. Mesothelin-targeted CARs: driving T cells to solid tumors[J]. Cancer Discov, 2016, 6(2): 133-146. DOI: 10.1158/2159-8290.CD-15-0583.

[26] CORTI C, VENETIS K, SAJJADI E, *et al*. CAR-T cell therapy for triple-negative breast cancer and other solid tumors: preclinical and clinical progress[J]. Expert Opin Investig Drugs, 2022, 31(6): 593-605. DOI: 10.1080/13543784.2022.2054326.

[27] MAJZNER R G, MACKALL C L. Tumor antigen escape from CAR T-cell therapy[J]. Cancer Discov, 2018, 8(10): 1219-1226. DOI: 10.1158/2159-8290.CD-18-0442.

[28] LABANIEH L, MACKALL C L. CAR immune cells: design principles, resistance and the next generation[J]. Nature, 2023, 614 (7949): 635-648. DOI: 10.1038/s41586-023-05707-3.

[29] NGUYEN D T, OGANDO-RIVAS E, LIU R X, *et al*. CAR T cell locomotion in solid tumor microenvironment[J/OL]. Cells, 2022, 11 (12): 1974[2025-02-10]. https://pubmed. ncbi. nlm. nih. gov/35741103/. DOI: 10.3390/cells11121974.

[30] MOON E K, WANG L C, DOLFI D V, *et al*. Multifactorial T-cell hypofunction that is reversible can limit the efficacy of chimeric antigen receptor-transduced human T cells in solid tumors[J]. Clin Cancer Res, 2014, 20(16): 4262-4273. DOI: 10.1158/1078-0432.CCR-13-2627.

[31] MA S, LI X C, WANG X Y, *et al*. Current progress in CAR-T cell therapy for solid tumors[J]. Int J Biol Sci, 2019, 15(12): 2548-2560. DOI: 10.7150/ijbs.34213.

[32] GUMBER D, WANG L D. Improving CAR-T immunotherapy: overcoming the challenges of T cell exhaustion[J/OL]. eBioMedicine, 2022, 77: 103941[2025-02-10]. http://dx. doi. org/10.1016/j.ebiom.2022.103941. DOI: 10.1016/j.ebiom.2022.103941.

[33] JOHN L B, DEVAUD C, DUONG C P M, *et al*. Anti-PD-1 antibody therapy potently enhances the eradication of established tumors by gene-modified T cells[J]. Clin Cancer Res, 2013, 19(20): 5636-5646. DOI: 10.1158/1078-0432.CCR-13-0458.

[34] LI S, SIRIWON N, ZHANG X Y, *et al.* Enhanced cancer immunotherapy by chimeric antigen receptor-modified T cells engineered to secrete checkpoint inhibitors[J]. Clin Cancer Res, 2017, 23(22): 6982-6992. DOI: 10.1158/1078-0432.CCR-17-0867.

[35] WANG L S, LO A, SCHOLLER J, *et al.* Targeting fibroblast activation protein in tumor stroma with chimeric antigen receptor T

cells can inhibit tumor growth and augment host immunity without severe toxicity[J]. Cancer Immunol Res, 2014, 2(2): 154-166. DOI: 10.1158/2326-6066.CIR-13-0027.

[36] CARUANA I, SAVOLDO B, HOYOS V, *et al*. Heparanase promotes tumor infiltration and antitumor activity of CAR-redirected T lymphocytes[J]. Nat Med, 2015, 21(5): 524-529. DOI: 10.1038/nm.3833.

[37] HUANG Z L, WU Y Q, ALLEN M E, *et al*. Engineering light-controllable CAR T cells for cancer immunotherapy[J/OL]. Sci Adv, 2020, 6(8): eaay9209[2025-02-10]. https://pubmed. ncbi. nlm. nih.gov/32128416/. DOI: 10.1126/sciadv.aay9209.

[38] PAN Y J, YOON S, SUN J, *et al*. Mechanogenetics for the remote and noninvasive control of cancer immunotherapy[J]. Proc Natl Acad Sci USA, 2018, 115(5): 992-997. DOI: 10.1073/pnas.1714900115.

[39] MILLER I C, ZAMAT A, SUN L, *et al.* Enhanced intratumoural activity of CAR T cells engineered to produce immunomodulators under photothermal control[J]. Nat Biomed Eng, 2021, 5(11): 1348-1359. DOI: 10.1038/s41551-021-00781-2.

[40] JUILLERAT A, MARECHAL A, FILHOL J M, *et al*. An oxygen sensitive self-decision making engineered CAR T-cell[J/OL]. Sci Rep, 2017, 7: 39833[2025-02-10]. https://pubmed.ncbi.nlm.nih.gov/28106050/. DOI: 10.1038/srep39833.

[41] LIAO Q B, HE H, MAO Y Y, *et al*. Engineering T cells with hypoxia-inducible chimeric antigen receptor (HiCAR) for selective tumor killing[J/OL]. Biomark Res, 2020, 8(1): 56[2025-02-10]. https://pubmed.ncbi.nlm.nih.gov/33292642/. DOI: 10.1186/s40364-020-00238-9.

[42] SHIRZADIAN M, MOORI S, RABBANI R, *et al*. SynNotch CAR-T cell, when synthetic biology and immunology meet again[J/OL]. Front Immunol, 2025, 16: 1545270[2025-02-10]. https://pubmed.ncbi.nlm.nih.gov/40308611/. DOI: 10.3389/fimmu.2025.1545270.

[43] ROYBAL K T, RUPP L J, MORSUT L, *et al*. Precision tumor recognition by T cells with combinatorial antigen-sensing circuits [J]. Cell, 2016, 164(4): 770-779. DOI: 10.1016/j.cell.2016.01.011.

[44] HERNANDEZ-LOPEZ R A, YU W, CABRAL K A, *et al*. T cell circuits that sense antigen density with an ultrasensitive threshold [J]. Science, 2021, 371(6534): 1166-1171. DOI: 10.1126/science.abc1855.

[45] ZHU I, LIU R, GARCIA J M, *et al*. Modular design of synthetic receptors for programmed gene regulation in cell therapies[J]. Cell, 2022, 185(8): 1431-1443. DOI: 10.1016/j.cell.2022.03.023.

[46] WU Y Q, HUANG Z L, LIU Y H, *et al*. Ultrasound control of genomic regulatory toolboxes for cancer immunotherapy[J/OL]. Nat Commun, 2024, 15(1): 10444[2025-02-10]. https://pubmed.ncbi.nlm.nih.gov/39617755/. DOI: 10.1038/s41467-024-54477-7.

[47] HERNÁNDEZ-LÓPEZ R A, KESTI T, MÄKELÄ A R, *et al*. Engineered SH3-derived sherpabodies function as a modular platform for targeted T-cell immunotherapy[J]. Cancer Res, 2025, 85(10): 1874-1887. DOI: 10.1158/0008-5472.CAN-24-1959.

[48] HONAKER Y, GRUBER D, JACOBS C, *et al*. Targeting human plasma cells using regulated BCMA CAR T cells eliminates circulating antibodies in humanized mice[J/OL]. Mol Ther, 2024: S1525-16(24)00817-7[2024-02-10]. https://pubmed. ncbi. nlm. nih.gov/39673129/. DOI: 10.1016/j.ymthe.2024.12.018.

[49] WU C Y, ROYBAL K T, PUCHNER E M, *et al*. Remote control of therapeutic T cells through a small molecule-gated chimeric receptor [J/OL]. Science, 2015, 350(6258): aab4077[2025-02-10]. https://pubmed. ncbi. nlm. nih. gov/26405231/. DOI: 10.1126/science.aab4077.

[50] LEUNG W H, GAY J, MARTIN U, *et al*. Sensitive and adaptable pharmacological control of CAR T cells through extracellular receptor dimerization[J/OL]. JCI Insight, 2019, 5(11): e124430 [2025-02-10]. https://pubmed. ncbi. nlm. nih. gov/31039141/. DOI: 10.1172/jci.insight.124430.

[51] JUILLERAT A, MARECHAL A, FILHOL J M, *et al*. Design of chimeric antigen receptors with integrated controllable transient functions[J/OL]. Sci Rep, 2016, 6: 18950[2025-02-10]. https://pubmed.ncbi.nlm.nih.gov/26750734/. DOI: 10.1038/srep18950.

[52] FOSTER A E, MAHENDRAVADA A, SHINNERS N P, *et al*. Regulated expansion and survival of chimeric antigen receptor-modified T cells using small molecule-dependent inducible MyD88/CD40[J]. Mol Ther, 2017, 25(9): 2176-2188. DOI: 10.1016/j.ymthe.2017.06.014.

[53] JAN M, SCARFÒ I, LARSON R C, *et al*. Reversible ON- and OFF-switch chimeric antigen receptors controlled by lenalidomide[J/OL]. Sci Transl Med, 2021, 13(575): eabb6295[2025-02-10]. https://pubmed.ncbi.nlm.nih.gov/33408186/. DOI: 10.1126/scitranslmed.abb6295.

[54] NGUYEN N T, HUANG K, ZENG H X, *et al.* Nano-optogenetic engineering of CAR T cells for precision immunotherapy with enhanced safety[J]. Nat Nanotechnol, 2021, 16(12): 1424-1434. DOI: 10.1038/s41565-021-00982-5.

[55] WANG X Y, MENG F Y, LI X, *et al*. Nanomodified switch induced precise and moderate activation of CAR-T cells for solid tumors[J/OL]. Adv Sci (Weinh), 2023, 10(12): e2205044[2025-02-10]. https://pubmed. ncbi. nlm. nih. gov/36755195/. DOI: 10.1002/advs.202205044.

[56] HAN X L, BRYSON P D, ZHAO Y F, *et al*. Masked chimeric antigen receptor for tumor-specific activation[J]. Mol Ther, 2017, 25 (1): 274-284. DOI: 10.1016/j.ymthe.2016.10.011.

[57] BORDIGNON C, BONINI C, VERZELETTI S, *et al*. Transfer of the HSV-tk gene into donor peripheral blood lymphocytes for *in vivo* modulation of donor anti-tumor immunity after allogeneic bone marrow transplantation[J]. Hum Gene Ther, 1995, 6(6): 813-819. DOI: 10.1089/hum.1995.6.6-813.

[58] STAVROU M, PHILIP B, TRAYNOR-WHITE C, *et al*. A rapamycin-activated caspase 9-based suicide gene[J]. Mol Ther, 2018, 26(5): 1266-1276. DOI: 10.1016/j.ymthe.2018.03.001.

[59] DI STASI A, TEY S K, DOTTI G, *et al*. Inducible apoptosis as a safety switch for adoptive cell therapy[J]. N Engl J Med, 2011, 365 (18): 1673-1683. DOI: 10.1056/NEJMoa1106152.

[60] GARGETT T, BROWN M P. The inducible caspase-9 suicide gene system as a "safety switch" to limit on-target, off-tumor toxicities of chimeric antigen receptor T cells[J/OL]. Front Pharmacol, 2014, 5: 235[2025-02-10]. https://pubmed. ncbi. nlm. nih. gov/25389405/. DOI: 10.3389/fphar.2014.00235.

[61] BOUQUET L, BÔLE-RICHARD E, WARDA W, *et al*. RapaCaspase-9-based suicide gene applied to the safety of IL-1RAP CAR-T cells[J]. Gene Ther, 2023, 30(9): 706-713. DOI: 10.1038/s41434-023-00404-2.

[62] THOMIS D C, MARKTEL S, BONINI C, *et al*. A Fas-based

suicide switch in human T cells for the treatment of graft-versus-host disease[J]. Blood, 2001, 97(5): 1249-1257. DOI: 10.1182/blood.v97.5.1249.

[63] DUONG M T, COLLINSON-PAUTZ M R, MORSCHL E, *et al*. Two-dimensional regulation of CAR-T cell therapy with orthogonal switches[J]. Mol Ther Oncolytics, 2018, 12: 124-137. DOI: 10.1016/j.omto.2018.12.009.

[64] TASIAN S K, KENDERIAN S S, SHEN F, *et al*. Optimized depletion of chimeric antigen receptor T cells in murine xenograft models of human acute myeloid leukemia[J]. Blood, 2017, 129(17): 2395-2407. DOI: 10.1182/blood-2016-08-736041.

[65] PASZKIEWICZ P J, FRÄßLE S P, SRIVASTAVA S, *et al*. Targeted antibody-mediated depletion of murine CD19 CAR T cells permanently reverses B cell aplasia[J]. J Clin Invest, 2016, 126(11): 4262-4272. DOI: 10.1172/JCI84813.

[66] MESTERMANN K, GIAVRIDIS T, WEBER J, *et al*. The tyrosine kinase inhibitor dasatinib acts as a pharmacologic on/off switch for CAR T cells[J/OL]. Sci Transl Med, 2019, 11(499): eaau5907[2025-02-10]. https://pubmed.ncbi.nlm.nih.gov/31270272/. DOI: 10.1126/scitranslmed.aau5907.

[67] WEBER E W, LYNN R C, SOTILLO E, *et al*. Pharmacologic control of CAR-T cell function using dasatinib[J]. Blood Adv, 2019, 3(5): 711-717. DOI: 10.1182/bloodadvances.2018028720.

[68] BAUR K, HEIM D, BEERLAGE A, *et al*. Dasatinib for treatment of CAR T-cell therapy-related complications[J/OL]. J Immunother Cancer, 2022, 10(12): e005956[2025-02-10]. https://pubmed.ncbi.nlm.nih.gov/36455991/. DOI: 10.1136/jitc-2022-005956.

[69] KARLSSON H, SVENSSON E, GIGG C, *et al*. Evaluation of intracellular signaling downstream chimeric antigen receptors[J/OL]. PLoS One, 2015, 10(12): e0144787[2025-02-10]. https://pubmed.ncbi.nlm.nih.gov/26700307/. DOI: 10.1371/journal.pone.0144787.

[70] JUILLERAT A, TKACH D, BUSSER B W, *et al*. Modulation of chimeric antigen receptor surface expression by a small molecule switch[J/OL]. BMC Biotechnol, 2019, 19(1): 44[2025-02-10]. https://pubmed.ncbi.nlm.nih.gov/31269942/. DOI: 10.1186/s12896-019-0537-3.

[71] SAHILLIOGLU A C, TOEBES M, APRIAMASHVILI G, *et al*. CRASH-IT switch enables reversible and dose-dependent control of TCR and CAR T-cell function[J]. Cancer Immunol Res, 2021, 9(9): 999-1007. DOI: 10.1158/2326-6066.CIR-21-0095.

[72] BÉKÉS M, LANGLEY D R, CREWS C M. PROTAC targeted protein degraders: the past is prologue[J]. Nat Rev Drug Discov, 2022, 21(3): 181-200. DOI: 10.1038/s41573-021-00371-6.

[73] LI Y Y, WU Y K, GAO S H, *et al*. PROTAC delivery in tumor immunotherapy: Where are we and where are we going?[J]. J Control Release, 2025, 378: 116-144. DOI: 10.1016/j.jconrel.2024.11.076.

[74] LEI K J, LI J Y, TU Z W, *et al*. Endosome-microautophagy targeting Chimera (eMIATAC) for targeted proteins degradation and enhance CAR-T cell anti-tumor therapy[J]. Theranostics, 2024, 14(11): 4481-4498. DOI: 10.7150/thno.98574.

[75] STRIJKER J G M, PASCUAL-PASTO G, GROTHUSEN G P, *et al*. Blocking MIF secretion enhances CAR T-cell efficacy against neuroblastoma[J/OL]. Eur J Cancer, 2025, 218: 115263[2025-02-10]. https://pubmed.ncbi.nlm.nih.gov/39908652/. DOI: 10.1016/j.ejca.2025.115263.

[76] LEE S M, KANG C H, CHOI S U, *et al*. A chemical switch system to modulate chimeric antigen receptor T cell activity through proteolysis-targeting Chimaera technology[J]. ACS Synth Biol, 2020, 9(5): 987-992. DOI: 10.1021/acssynbio.9b00476.

[77] GIORDANO-ATTIANESE G, GAINZA P, GRAY-GAILLARD E, *et al*. A computationally designed chimeric antigen receptor provides a small-molecule safety switch for T-cell therapy[J]. Nat Biotechnol, 2020, 38(4): 426-432. DOI: 10.1038/s41587-019-0403-9.

[78] HOTBLACK A, KOKALAKI E K, PALTON M J, *et al*. Tunable control of CAR T cell activity through tetracycline mediated disruption of protein-protein interaction[J/OL]. Sci Rep, 2021, 11(1): 21902[2025-02-10]. https://pubmed.ncbi.nlm.nih.gov/34754016/. DOI: 10.1038/s41598-021-01418-9.

[79] FEDOROV V D, THEMELI M, SADELAIN M. PD-1- and CTLA-4-based inhibitory chimeric antigen receptors (iCARs) divert off-target immunotherapy responses[J/OL]. Sci Transl Med, 2013, 5(215): 215ra172[2025-02-10]. https://pubmed.ncbi.nlm.nih.gov/24337479/. DOI: 10.1126/scitranslmed.3006597.

[80] RICHARDS R M, ZHAO F F, FREITAS K A, *et al*. NOT-gated CD93 CAR T cells effectively target AML with minimized endothelial cross-reactivity[J]. Blood Cancer Discov, 2021, 2(6): 648-665. DOI: 10.1158/2643-3230.BCD-20-0208.

[81] PARK H B, KIM K H, KIM J H, *et al*. Improved safety of chimeric antigen receptor T cells indirectly targeting antigens via switchable adapters[J/OL]. Nat Commun, 2024, 15(1): 9917[2025-02-10]. https://pubmed.ncbi.nlm.nih.gov/39557825/. DOI: 10.1038/s41467-024-53996-7.

[82] BANGAYAN N J, WANG L, BURTON SOJO G, *et al*. Dual-inhibitory domain iCARs improve the efficiency of the AND-NOT gate CAR T strategy[J/OL]. Proc Natl Acad Sci USA, 2023, 120(47): e2312374120[2025-02-10]. https://pubmed.ncbi.nlm.nih.gov/37963244/. DOI: 10.1073/pnas.2312374120.

[83] KIM M S, MA J S Y, YUN H, *et al*. Redirection of genetically engineered CAR-T cells using bifunctional small molecules[J]. J Am Chem Soc, 2015, 137(8): 2832-2835. DOI: 10.1021/jacs.5b00106.

[84] TAMADA K, GENG D G, SAKODA Y, *et al*. Redirecting gene-modified T cells toward various cancer types using tagged antibodies[J]. Clin Cancer Res, 2012, 18(23): 6436-6445. DOI: 10.1158/1078-0432.CCR-12-1449.

[85] CHU W Q, ZHOU Y X, TANG Q, *et al*. Bi-specific ligand-controlled chimeric antigen receptor T-cell therapy for non-small cell lung cancer[J]. Biosci Trends, 2018, 12(3): 298-308. DOI: 10.5582/bst.2018.01048.

[86] PARRA-NIETO J, HIDALGO L, MÁRQUEZ-CANTUDO M, *et al*. Liposomal-based nanoarchitectonics as bispecific T cell engagers in neuroblastoma therapy[J]. ACS Appl Mater Interfaces, 2025, 17(8): 11937-11945. DOI: 10.1021/acsami.5c00633.

[87] ABUDUREHEMAN T, ZHOU H, YANG L T, *et al*. Construction of switch modules for CAR-T cell treatment using a site-specific conjugation system[J]. Bioconjug Chem, 2024, 35(5): 604-615. DOI: 10.1021/acs.bioconjchem.4c00050.

[88] CAO Y J, WANG X C, WANG Z D, *et al*. Switchable CAR-T cells outperformed traditional antibody-redirected therapeutics targeting

breast cancers[J]. ACS Synth Biol, 2021, 10(5): 1176-1183. DOI: 10.1021/acssynbio.1c00007.

[89] PELLEGRINO C, FAVALLI N, VOLTA L, *et al*. Peptide-guided adaptor-CAR T-Cell therapy for the treatment of SSTR2-expressing neuroendocrine tumors[J/OL]. Oncoimmunology, 2024, 13(1): 2412371[2025-02-10]. https://pubmed.ncbi.nlm.nih.gov/39376579/. DOI: 10.1080/2162402X.2024.2412371.

[90] LU Y J, CHU H Y, WHEELER L W, *et al*. Preclinical evaluation of bispecific adaptor molecule controlled folate receptor CAR-T cell therapy with special focus on pediatric malignancies[J/OL]. Front Oncol, 2019, 9: 151[2025-02-10]. https://pubmed.ncbi.nlm.nih.gov/30941303/. DOI: 10.3389/fonc.2019.00151.

[91] ZHANG B, WANG Y, HUANG S L, *et al*. Photoswitchable CAR-T cell function *in vitro* and *in vivo via* a cleavable mediator[J]. Cell Chem Biol, 2021, 28(1): 60-69. DOI: 10.1016/j.chembiol.2020.10.004.

[92] KOBAYASHI A, NOBILI A, NEIER S C, *et al*. Light-controllable binary switch activation of CAR T cells[J/OL]. ChemMedChem, 2022, 17(12): e202100722[2025-02-10]. https://pubmed.ncbi.nlm.nih.gov/35146940/. DOI: 10.1002/cmdc.202100722.

[93] RODGERS D T, MAZAGOVA M, HAMPTON E N, *et al*. Switch-mediated activation and retargeting of CAR-T cells for B-cell malignancies[J/OL]. Proc Natl Acad Sci USA, 2016, 113(4): E459-E468[2025-02-10]. https://pubmed.ncbi.nlm.nih.gov/26759369/. DOI: 10.1073/pnas.1524155113.

[94] VIAUD S, MA J S Y, HARDY I R, *et al*. Switchable control over *in vivo* CAR T expansion, B cell depletion, and induction of memory [J/OL]. Proc Natl Acad Sci USA, 2018, 115(46): E10898-E10906 [2025-02-10]. https://pubmed.ncbi.nlm.nih.gov/30373813/. DOI: 10.1073/pnas.1810060115.

[95] KORISTKA S, CARTELLIERI M, ARNDT C, *et al*. Retargeting of regulatory T cells to surface-inducible autoantigen La/SS-B[J]. J Autoimmun, 2013, 42: 105-116. DOI: 10.1016/j.jaut.2013.01.002.

[96] CARTELLIERI M, FELDMANN A, KORISTKA S, *et al*. Switching CAR T cells on and off: a novel modular platform for retargeting of T cells to AML blasts[J/OL]. Blood Cancer J, 2016, 6 (8): e458[2025-02-10]. https://pubmed.ncbi.nlm.nih.gov/27518241/. DOI: 10.1038/bcj.2016.61.

[97] RAJ D, YANG M H, RODGERS D, *et al*. Switchable CAR-T cells mediate remission in metastatic pancreatic ductal adenocarcinoma[J]. Gut, 2019, 68(6): 1052-1064. DOI: 10.1136/gutjnl-2018-316595.

[98] SALIU M A, WANG Q, SALISU M D, *et al*. Mesothelin-targeted CAR-T cells secreting NKG2D-BiTEs exhibit potent efficacy against triple-negative breast cancer[J/OL]. Exp Hematol Oncol, 2025, 14(1): 27[2025-02-10]. https://pubmed.ncbi.nlm.nih.gov/40033418/. DOI: 10.1186/s40164-025-00621-y.

[99] URBANSKA K, LYNN R C, STASHWICK C, et al. Targeted cancer immunotherapy *via* combination of designer bispecific antibody and novel gene-engineered T cells[J/OL]. J Transl Med, 2014, 12: 347[2025-2-10]. https://pubmed.ncbi.nlm.nih.gov/25496493/. DOI: 10.1186/s12967-014-0347-2.

[100] AMBROSE C, SU L H, WU L, *et al*. Abstract 3768: CAR T cells specific for CD19 can be redirected to kill CD19 negative tumors [J/OL]. Cancer Res, 2017, 77(13_Supplement): 3768[2025-02-10]. https://doi.org/10.1158/1538-7445.am2017-3768. DOI: 10.1158/1538-7445.am2017-3768.

[101] CHOI B D, YU X L, CASTANO A P, *et al*. CAR-T cells secreting BiTEs circumvent antigen escape without detectable toxicity[J]. Nat Biotechnol, 2019, 37(9): 1049-1058. DOI: 10.1038/s41587-019-0192-1.

[102] URBANSKA K, POWELL D J. Development of a novel universal immune receptor for antigen targeting: To Infinity and beyond[J]. Oncoimmunology, 2012, 1(5): 777-779. DOI: 10.4161/onci.19730.

[103] URBANSKA K, LANITIS E, POUSSIN M, *et al*. A universal strategy for adoptive immunotherapy of cancer through use of a novel T-cell antigen receptor[J]. Cancer Res, 2012, 72(7): 1844-1852. DOI: 10.1158/0008-5472.CAN-11-3890.

[104] LOHMUELLER J J, HAM J D, KVORJAK M, *et al*. mSA2 affinity-enhanced biotin-binding CAR T cells for universal tumor targeting[J/OL]. Oncoimmunology, 2017, 7(1): e1368604[2025-02-10]. https://pubmed.ncbi.nlm.nih.gov/29296519/. DOI: 10.1080/2162402X.2017.1368604.

[105] WERCHAU N, KOTTER B, CRIADO-MORONATI E, *et al*. Combined targeting of soluble latent TGF-β and a solid tumor-associated antigen with adapter CAR T cells[J/OL]. Oncoimmunology, 2022, 11(1): 2140534[2025-02-10]. https://pubmed.ncbi.nlm.nih.gov/36387056/. DOI: 10.1080/2162402X.2022.2140534.

[106] MINUTOLO N G, SHARMA P, POUSSIN M, *et al*. Quantitative control of gene-engineered T-cell activity through the covalent attachment of targeting ligands to a universal immune receptor[J]. J Am Chem Soc, 2020, 142(14): 6554-6568. DOI: 10.1021/jacs.9b11622.

[107] LIU X, WEN J Y, YI H L, *et al*. Split chimeric antigen receptor-modified T cells targeting glypican-3 suppress hepatocellular carcinoma growth with reduced cytokine release[J/OL]. Ther Adv Med Oncol, 2020, 12: 1758835920910347[2025-02-10]. https://pubmed.ncbi.nlm.nih.gov/32215059/. DOI: 10.1177/1758835920910347.

[108] CARDLE I I, SCHERER D R, JENSEN M C, *et al*. *In situ* bioconjugation of synthetic peptides onto universal chimeric antigen receptor T cells for targeted cancer immunotherapies[J]. ACS Nano, 2025, 19(5): 5750-5768. DOI: 10.1021/acsnano.4c16824.

[109] STEPANOV A V, KALININ R S, SHIPUNOVA V O, *et al*. Switchable targeting of solid tumors by BsCAR T cells[J/OL]. Proc Natl Acad Sci USA, 2022, 119(46): e2210562119[2025-02-10]. https://pubmed.ncbi.nlm.nih.gov/36343224/. DOI: 10.1073/pnas.2210562119.

[110] ZAKERI B, FIERER J O, CELIK E, *et al*. Peptide tag forming a rapid covalent bond to a protein, through engineering a bacterial adhesin[J/OL]. Proc Natl Acad Sci USA, 2012, 109(12): E690-E697[2025-02-10]. https://pubmed.ncbi.nlm.nih.gov/22366317/. DOI: 10.1073/pnas.1115485109.

[111] BUCKLE A M, SCHREIBER G, FERSHT A R. Protein-protein recognition: crystal structural analysis of a barnase-barstar complex at 2.0-a resolution[J]. Biochemistry, 1994, 33(30): 8878-8889. DOI: 10.1021/bi00196a004.

[112] DEYEV S M, WAIBEL R, LEBEDENKO E N, *et al*. Design of multivalent complexes using the barnase*barstar module[J]. Nat Biotechnol, 2003, 21(12): 1486-1492. DOI: 10.1038/nbt916.

[113] RADER C. Chemically programmed antibodies[J]. Trends Biotechnol, 2014, 32(4): 186-197. DOI: 10.1016/j.tibtech.2014.02.003.

[114] STEPANOV A V, XIE J, ZHU Q Q, *et al*. Control of the antitumour activity and specificity of CAR T cells *via* organic adapters covalently tethering the CAR to tumour cells[J]. Nat Biomed Eng, 2024, 8(5): 529-543. DOI: 10.1038/s41551-023-01102-5.

[115] CHO J H, COLLINS J J, WONG W W. Universal chimeric antigen receptors for multiplexed and logical control of T cell responses[J]. Cell, 2018, 173(6): 1426-1438. DOI: 10.1016/j.cell.2018.03.038.

[116] RUFFO E, BUTCHY A A, TIVON Y, *et al*. Post-translational covalent assembly of CAR and synNotch receptors for programmable antigen targeting[J/OL]. Nat Commun, 2023, 14 (1): 2463[2025-02-10]. https://pubmed. ncbi. nlm. nih. gov/37160880/. DOI: 10.1038/s41467-023-37863-5.

[117] CHO J H, OKUMA A, SOFJAN K, *et al*. Engineering advanced logic and distributed computing in human CAR immune cells[J/OL]. Nat Commun, 2021, 12(1): 792[2025-02-10]. https://pubmed.ncbi.nlm.nih.gov/33542232/. DOI: 10.1038/s41467-021-21078-7.

[118] PINTO S, PAHL J, SCHOTTELIUS A, *et al*. Reimagining antibody-dependent cellular cytotoxicity in cancer: the potential of natural killer cell engagers[J]. Trends Immunol, 2022, 43(11): 932-946. DOI: 10.1016/j.it.2022.09.007.

[119] CLÉMENCEAU B, CONGY-JOLIVET N, GALLOT G, *et al*. Antibody-dependent cellular cytotoxicity (ADCC) is mediated by genetically modified antigen-specific human T lymphocytes[J]. Blood, 2006, 107(12): 4669-4677. DOI: 10.1182/blood-2005-09-3775.

[120] KUDO K, IMAI C, LORENZINI P, *et al*. T lymphocytes expressing a CD16 signaling receptor exert antibody-dependent cancer cell killing[J]. Cancer Res, 2014, 74(1): 93-103. DOI: 10.1158/0008-5472.CAN-13-1365.

[121] ZHAO J J, CHEN M L, LI X D, *et al*. Construction and characterization of chimeric FcγR T cells for universal T cell therapy[J/OL]. Exp Hematol Oncol, 2025, 14(1): 6[2025-02-10]. https://pubmed. ncbi. nlm. nih. gov/39810257/. DOI: 10.1186/s40164-025-00595-x.

[122] ZHU W, WANG Y, LV L Y, *et al*. Universal chimeric Fc γ receptor T cells with appropriate affinity for IgG1 antibody exhibit optimal antitumor efficacy[J]. Acta Pharm Sin B, 2023, 13(5): 2071-2085. DOI: 10.1016/j.apsb.2023.02.004.

[123] DALE G L, GADDY P, PIKUL F J. Antibodies against biotinylated proteins are present in normal human serum[J]. J Lab Clin Med, 1994, 123(3): 365-371.

[124] JHAWAR S R, THANDONI A, BOMMAREDDY P K, *et al.* Oncolytic viruses-natural and genetically engineered cancer immunotherapies[J/OL]. Front Oncol, 2017, 7: 202[2025-02-10]. https://pubmed. ncbi. nlm. nih. gov/28955655/. DOI: 10.3389/fonc.2017.00202.

[125] MARELLI G, HOWELLS A, LEMOINE N R, *et al*. Oncolytic viral therapy and the immune system: a double-edged sword against cancer[J/OL]. Front Immunol, 2018, 9: 866[2025-02-10]. https://pubmed. ncbi. nlm. nih. gov/29755464/. DOI: 10.3389/fimmu.2018.00866.

[126] CHEN C, PARK A K, MONROY I, *et al*. Using oncolytic virus to retask CD19-chimeric antigen receptor T cells for treatment of pancreatic cancer: toward a universal chimeric antigen receptor T-cell strategy for solid tumor[J]. J Am Coll Surg, 2024, 238(4): 436-447. DOI: 10.1097/xcs.0000000000000964.

[127] AALIPOUR A, LE BOEUF F, TANG M, *et al*. Viral delivery of CAR targets to solid tumors enables effective cell therapy[J]. Mol Ther Oncolytics, 2020, 17: 232-240. DOI: 10.1016/j.omto.2020.03.018.

[128] PARK A K, FONG Y, KIM S I, *et al*. Effective combination immunotherapy using oncolytic viruses to deliver CAR targets to solid tumors[J/OL]. Sci Transl Med, 2020, 12(559): eaaz1863 [2025-02-10]. https://pubmed. ncbi. nlm. nih. gov/32878978/. DOI: 10.1126/scitranslmed.aaz1863.

[129] LIU Y Y, ZHENG Y X, DENG T Y, *et al*. Oncolytic herpes simplex virus delivery of dual CAR targets of CD19 and BCMA as well as immunomodulators to enhance therapeutic efficacy in solid tumors combined with CAR T cell therapy[J/OL]. Front Oncol, 2022, 12: 1037934[2025-02-10]. https://pubmed. ncbi. nlm. nih.gov/36353540/. DOI: 10.3389/fonc.2022.1037934.

[130] SUN Z C, LI R T, SHEN Y, *et al*. *In situ* antigen modification-based target-redirected universal chimeric antigen receptor T (TRUE CAR-T) cell therapy in solid tumors[J/OL]. J Hematol Oncol, 2022, 15(1): 29[2025-02-10]. https://pubmed.ncbi.nlm.nih.gov/35303900/. DOI: 10.1186/s13045-022-01246-y.

[131] ZHANG A Q, HOSTETLER A, CHEN L E, *et al.* Universal redirection of CAR T cells against solid tumours via membrane-inserted ligands for the CAR[J]. Nat Biomed Eng, 2023, 7(9): 1113-1128. DOI: 10.1038/s41551-023-01048-8.

[132] FAN J X, HU Z B, GU H Y, *et al*. Tumor cell membrane remodeling with universal ligand for CAR-T cells to inhibit solid tumors[J]. Sci China Chem, 2023, 66(11): 3223-3231. DOI: 10.1007/s11426-023-1796-0.

[133] GARIN-CHESA P, OLD L J, RETTIG W J. Cell surface glycoprotein of reactive stromal fibroblasts as a potential antibody target in human epithelial cancers[J]. Proc Natl Acad Sci USA, 1990, 87(18): 7235-7239. DOI: 10.1073/pnas.87.18.7235.

[134] BUGHDA R, DIMOU P, D'SOUZA R R, *et al* Fibroblast activation protein (FAP) -targeted CAR-T cells: launching an attack on tumor stroma[J]. Immunotargets Ther, 2021, 10: 313-323. DOI: 10.2147/ITT.S291767.

[135] LO A, WANG L S, SCHOLLER J, *et al*. Tumor-promoting desmoplasia is disrupted by depleting FAP-expressing stromal cells [J]. Cancer Res, 2015, 75(14): 2800-2810. DOI: 10.1158/0008-5472.CAN-14-3041.

[136] VINCENT R L, GURBATRI C R, LI F D, *et al*. Probiotic-guided CAR-T cells for solid tumor targeting[J]. Science, 2023, 382 (6667): 211-218. DOI: 10.1126/science.add7034.

[137] ZHENG R, SHEN K, LIANG S X, *et al*. Specific ECM degradation potentiates the antitumor activity of CAR-T cells in solid tumors[J]. Cell Mol Immunol, 2024, 21(12): 1491-1504. DOI: 10.1038/s41423-024-01228-9.

［收稿日期］ 2025-02-10 ［修回日期］ 2025-04-25
［本文编辑］ 向正华，黄静怡