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· 综述 ·

先天免疫细胞在 CAR-T 治疗中的作用研究进展

查晨宇[1,2]，王迎[1,2]*
[1]中国医学科学院血液病医院（中国医学科学院血液学研究所），血液与健康全国重点实验室，国家血液系统疾病临床医学研究中心，细胞生态海河实验室，天津 300020
[2]天津医学健康研究院，天津 301600

摘要：嵌合抗原受体 T（CAR-T）细胞疗法在血液系统恶性肿瘤治疗中取得了突破性进展，但其长期疗效仍面临细胞持久性不足、肿瘤微环境抑制等多重挑战。近年来研究显示，CAR-T 细胞的功能受到宿主先天免疫系统的调控，二者之间存在复杂的相互作用网络。本综述旨在系统阐述先天免疫细胞在 CAR-T 治疗中的双重角色，总结通过靶向或重编程先天免疫细胞以增强 CAR-T 疗效的最新策略，并对未来协同先天与适应性免疫的下一代 CAR-T 疗法发展进行展望。

关键词：血液系统肿瘤；免疫治疗；嵌合抗原受体 T 细胞；先天免疫；肿瘤微环境
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Research progress on the role of innate immune cells in CAR-T therapy

ZHA Chenyu[1,2], WANG Ying[1,2]*
[1]State Key Laboratory of Experimental Hematology, National Clinical Research Center for Blood Diseases, Haihe Laboratory of Cell Ecosystem, Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Tianjin 300020, China
[2]Tianjin Institutes of Health Science, Tianjin 301600, China

Abstract: Chimeric antigen receptor T (CAR-T) cell therapy has achieved breakthrough progress in the treatment of hematologic malignancies, yet its long-term efficacy remains challenged by issues such as insufficient cell persistence and the immunosuppressive tumor microenvironment. Recent studies have revealed that CAR-T cell function is profoundly regulated by the host innate immune system, forming a complex interactive network between the two. This review systematically elucidates the dual roles of innate immune cells in CAR-T therapy, summarizes the latest strategies to enhance CAR-T efficacy by targeting or reprogramming innate immune cells, and offers perspectives on the development of next-generation CAR-T therapies that harness both innate and adaptive immunity.

Key words: Hematologic malignancies; Immunotherapy; Chimeric antigen receptor T cell; Innate immunity; Tumor microenvironment

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*通信作者

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* Corresponding author

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嵌合抗原受体 T(chimeric antigen receptor T, CAR-T)细胞疗法在治疗血液系统恶性肿瘤中取得了革命性突破[1-3],然而,其在血液肿瘤中的长期疗效,以及实体瘤中的治疗应答仍不尽如人意,面临诸多挑战:如 CAR-T 细胞在体内的持久性不足和功能耗竭、复杂的肿瘤免疫抑制微环境所形成的屏障等[4-5]。许多升级策略聚焦于 CAR-T 细胞本身,通过优化设计(如共刺激信号、基因修饰编辑等)来提升其功能[6-7]。然而,越来越多的证据表明,不能将 CAR-T 细胞视为体内的孤立组分。这些工程化细胞回输后,会浸润并运作于一个由宿主先天免疫系统主导的生态之中。

先天免疫细胞群体在肿瘤发展中发挥重要的多重作用。大体上将先天免疫细胞根据各自在肿瘤发生中的作用分为抗瘤群体与促瘤群体。抗瘤群体可直接非特异性杀伤肿瘤细胞,或者启动并维持适应性抗肿瘤免疫应答。而促瘤群体通过重塑肿瘤微环境,使之适应肿瘤生长(如血管化和缺氧等),或抑制抗肿瘤免疫促进肿瘤免疫逃逸[8-10]。此外,一些具有明显异质性及可塑性的先天免疫细胞可以在肿瘤微环境的复杂影响下扮演抗瘤与促瘤的双重角色[11-12]。利用抗瘤先天免疫细胞诱发更强的抗瘤免疫应答,或者靶向具有免疫抑制特性的先天免疫细胞群体是目前有前景的肿瘤治疗方式[10,13]。这些细胞也与回输的 CAR-T 细胞进行着持续的双向对话(图 1)。因此,全面理解 CAR-T 细胞与宿主先天免疫系统之间复杂的相互作用,对于开发基于先天与适应性免疫协同的下一代 CAR-T 疗法至关重要。本综述将梳理该领域的最新进展,阐述先天免疫细胞在 CAR-T 疗法中的双重作用,并展望通过调控这一互作网络来开发更高效、更持久的新型 CAR-T 治疗策略。

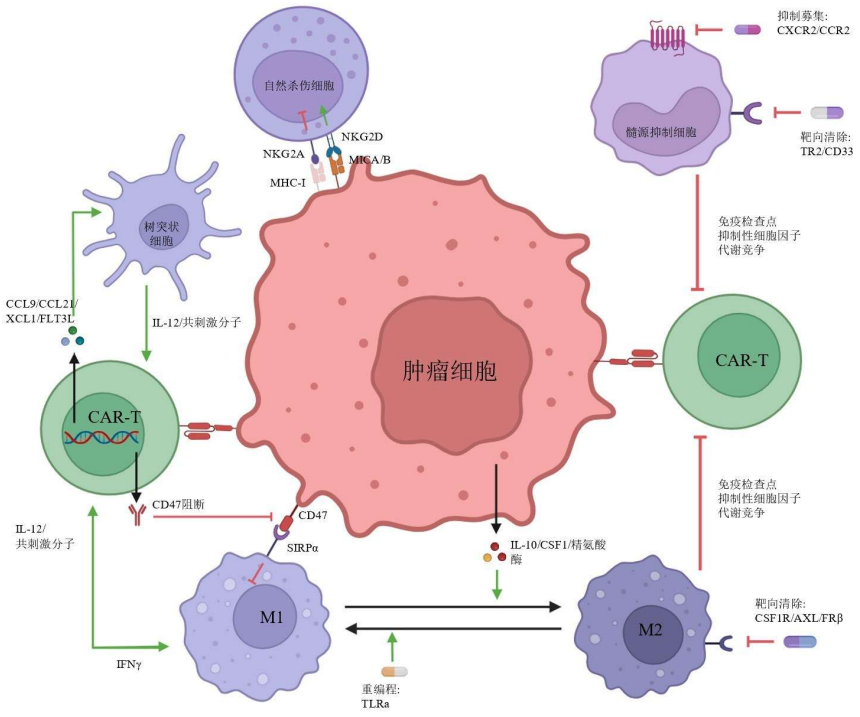


图 1 CAR-T 与先天免疫细胞的互作与靶向策略。CAR-T:嵌合抗原受体 T;CD:分化簇;CSF1:集落刺激因子 1;Flt3L:Fms 相关酪氨酸激酶 3 配体;FRβ:叶酸受体 β;IFNγ:干扰素 γ;IL:白细胞介素;MDSC:髓源抑制细胞;MHC-I:主要组织相容性复合体 I 类;MICA/B:MHC I 类相关链 A/B;NK:自然杀伤;NKG2A:自然杀伤细胞群 2A;NKG2D:自然杀伤细胞群 2D;SIRPα:信号调节蛋白 α;TLRα:Toll 样受体激动剂;TR2:肿瘤坏死因子相关凋亡诱导配体受体 2;XCL1:X-C 基序趋化因子配体 1。

Figure 1 CAR-T and innate immune cells interactions and targeting strategies. CAR-T: chimeric antigen receptor T; CD: cluster of differentiation; CSF1: colony-stimulating factor 1; Flt3L: Fms-related tyrosine kinase 3 ligand; FRβ: folate receptor β; IFNγ: interferon γ; IL: interleukin; MDSC: myeloid-derived suppressor cell; MHC-I: major histocompatibility complex class I; MICA/B: MHC class I-related chain A/B; NK: natural killer; NKG2A: natural killer group 2A; NKG2D: natural killer group 2D; SIRPα: signal regulatory protein α; TLRa: Toll-like receptor agonist; TR2: tumor necrosis factor-related apoptosis-inducing ligand receptor 2; XCL1: X-C motif chemokine ligand 1.

1　自然杀伤细胞

自然杀伤(natural killer, NK)细胞通过免疫监视与强力细胞毒性执行抗肿瘤功能。NK 细胞最重要的激活信号之一是肿瘤细胞上主要组织相容性复合体(major histocompatibility complex, MHC)-Ⅰ类分子的下调或丢失,这本是肿瘤细胞逃逸适应性免疫的一个重要机制,但这反而促成了 NK 细胞对肿瘤细胞的识别。这是由于 MHC-Ⅰ类分子的丢失使 NK 细胞上的抑制性 KIR 受体不再识别其配体,中断了抑制信号。此外,NK 细胞上激活受体以及黏附分子识别肿瘤细胞上相应配体的过程也参与 NK 细胞活化[14-16]。当激活信号主导时,NK 细胞便通过分泌毒性蛋白,表达死亡受体配体和调控适应性免疫等方式执行抗肿瘤功能[14-16]。

尽管 NK 细胞被赋予强力的抗肿瘤功能,但这一群体通常在血液肿瘤患者中表现出受抑制的状态,如激活受体下调、抑制受体上调、低毒细胞亚群扩增等。许多研究发现急性髓系白血病(acute myeloid leukemia, AML)患者体内的 NK 细胞会下调激活受体(如 NKG2D 等)[17-20],并且上调抑制受体(如 NKG2A 和免疫检查点等)[21-22],导致低毒低能表型的 NK 细胞群体扩增。类似的 NK 细胞低能状态也在多发性骨髓瘤(multiple myeloma, MM)患者骨髓微环境中发现[23]。在急性淋巴细胞白血病(acute lymphoblastic leukemia, ALL)患者中,NK 细胞表现为成熟障碍,如低毒性并产生大量细胞因子。低毒未成熟的 NK 细胞难以杀伤白血病细胞,反而增强钙离子信号并增加免疫检查点表达,导致过度激活并耗竭的 NK 细胞增多,这与 ALL 不良预后相关[24]。除了 NK 细胞异常之外,血液系统恶性细胞也可以通过下调 NK 细胞激活配体、上调 NK 细胞抑制配体等方式增加其对 NK 细胞的抗性[25-26]。此外,一些具有免疫抑制功能的髓系细胞也促成了 NK 细胞的功能障碍。总而言之,NK 细胞在血液肿瘤患者中展现出功能受损表型,重建 NK 细胞抗肿瘤功能在血液肿瘤免疫治疗中有重要意义。

鉴于 NK 细胞的抗肿瘤功能,利用 NK 细胞与 CAR-T 细胞之间的协同效应可能为患者提供临床益处。CAR-NK 与 CAR-T 联合疗法在疗效、持久性和安全性方面优于单独使用 CAR-NK 或 CAR-T[27]。另一项研究[28]发现,在 CAR-T 中添加 NK 细胞可重塑细胞因子谱,增加 T 细胞趋化细胞因子(CCL3 和 CCL5)的分泌。体内成像显示,NK 细胞加速了 CAR-T 向骨髓瘤细胞的迁移。此外,NK 细胞减轻了由暴露于骨髓瘤细胞引起的CAR-T 细胞衰老和耗竭。这些结果表明,联合施用CAR-T 和 NK 细胞建立了互补的肿瘤杀伤机制,包括抗原依赖性和非抗原依赖性方式。此外,这两种细胞类型之间通过共刺激分子和细胞因子介导的协同相互作用,可能增强 CAR-T 细胞的迁移、抗肿瘤疗效和持久性。有研究[29-31]还利用内源性 NK 细胞增强 CAR-T 疗效:通过工程化改造 CAR-T 细胞分泌炎性细胞因子〔如白细胞介素(interleukin, IL)-12、IL-15和 IL-18〕,这些修饰细胞可诱导肿瘤微环境中 NK 细胞的浸润和活化。在临床前研究中,此类具有细胞因子分泌能力的“装甲 CAR-T 细胞”优于传统 CAR-T,但其优势不仅源于内源性 NK 细胞的招募,更关键的是肿瘤免疫微环境的重塑。然而,也有研究揭示 NK 细胞的意外作用:其分泌的干扰素 γ(interferon γ, IFNγ)作用于肿瘤细胞以削弱 CAR-T疗效[32-33],而耗竭 NK 细胞反而增强CAR-T 的治疗效果[33]。但这些效应需进一步验证,因为可能存在肿瘤类型依赖性,且 NK 细胞并非 CAR-T 抑制的直接介导者。另一个 NK 细胞介导的对 CAR-T的负面影响涉及针对同种异体CAR-T产品的免疫排斥,这可能损害体内 CAR-T 的扩增。尽管宿主 T 细胞是排斥的主要驱动因素,但认识到 NK 细胞的作用仍至关重要,尤其考虑到清除 CAR-T上的 MHC-Ⅰ类分子(一种规避宿主 T 细胞排斥的主流策略)对宿主 NK 细胞靶向产生的影响未知[34]。目前,多项研究[35-39]提议对 CAR-T 细胞进行工程化修饰,例如敲除特定分子或过表达保护性分子,以使同种异体 CAR-T 产品逃逸 T 细胞和 NK 细胞介导的免疫排斥。然而,这些发现仍需临床验证。

临床研究中,多项针对 CAR-T 治疗后不同结局患者的研究显示,其 NK 细胞的表型与功能存在显著差异。具体表现为:MM 患者接受 B 细胞成熟抗原(B-cell maturation antigen, BCMA) CAR-T 治

疗后，复发时表达抑制性受体 TIGIT 的 NK 细胞较治疗前水平显著扩增[40]。这种差异早在治疗前就已显现：与复发/无应答患者相比，治疗应答者在 CAR-T 输注前 NK 细胞中的细胞毒性相关基因及趋化因子基因表达显著上调；而复发/无应答患者在 CAR-T 输注前后均呈现 CD56-强表达未成熟 NK 细胞的富集及免疫功能受损相关基因的高表达[41-42]。此外，更高数量的 NK 细胞与长期预后改善显著相关：有研究[43]发现 CAR-T 输注后 NK 细胞数量每增加 1 个对数级，B 细胞淋巴瘤患者死亡风险下降 0.52 倍。这些发现表明 NK 细胞对 CAR-T治疗患者结局具有潜在预测价值，但其影响疗效的具体作用机制仍需深入探索。

2 巨噬细胞

肿瘤相关巨噬细胞（tumor associated macrophage，TAM）在肿瘤免疫中扮演着复杂且高度可塑的角色，其功能表型呈现混合特征。目前广泛采用的 M1/M2 二分法虽可大致区分为抗瘤与促瘤表型，但不足以充分反映肿瘤微环境中巨噬细胞真实的异质性[44]。由于多数研究采用 M1/M2 分类，这里我们将沿用：M1 作为促炎抗肿瘤类型，可提呈肿瘤抗原激活适应性免疫，可释放活性氧、一氧化氮等物质直接杀伤肿瘤细胞，也可分泌促炎细胞因子；与之相反，抗炎促肿瘤 M2 型巨噬细胞则可通过表达免疫检查点、分泌抑制性细胞因子、消耗代谢物质、募集其他免疫抑制细胞等机制等机制直接或间接抑制抗肿瘤免疫[45-46]。

在血液肿瘤患者中，通常以 M2 型巨噬细胞占主导地位，并且 M2 的富集与不良预后相关[47-50]。研究[51-53]发现血液肿瘤及微环境成分可通过多种机制诱导 M2 型巨噬细胞极化，如肿瘤细胞分泌的 IL-10、集落刺激因子 1（colony-stimulating factor 1，CSF1）、精氨酸酶等可溶性分子。另外，Du 等[54]发现 AML 来源外泌体中的 circ_001264 siRNA 被单核细胞摄取后，可激活 p38-信号传导及转录活化因子 3（signal transducers and activators of transcription 3，STAT3）通路并诱导 M2 极化。Kim 等[55]发现 MYC/BCL2 双表达弥漫大 B 细胞淋巴瘤（diffuse large B cell lymphoma，DLBCL）可通过增强的 CCL2/CCR2 轴促进 M2 极化，形成免疫抑制环境。在 MM 中，Mougiakakos 等[56]则鉴定 IKZF1-IRF4/IRF5 轴参与调控 M2 极化，而降解 IKZF1 则可使巨噬细胞恢复 M1 样表型。以上研究表明血液肿瘤中 M2 极化的普遍倾向，以及其作为治疗靶点的潜力。

巨噬细胞与 CAR-T 的互作是 CAR-T 治疗中的关键因素。一方面，CAR-T 可分泌肿瘤坏死因子 α（tumor necrosis factor-α，TNF-α）、IFNγ 等细胞因子诱导 M1 极化，以发挥协同抗肿瘤作用[57-59]。另一方面，CAR-T 的活性同时受 M2 巨噬细胞制约，例如通过表达免疫检查点、分泌抑制性细胞因子等机制[60]。另外，Yan 等[61]研究揭示，M2 巨噬细胞可通过增强胆固醇外排，导致肿瘤微环境中间质胆固醇水平升高，进而抑制 TCR 信号通路并激活内质网应激反应，最终诱导 CAR-T 及其他 $CD8^+$ T 细胞耗竭。Stahl 等[62]则在 CAR-T 疗效不佳的淋巴瘤患者中鉴定出一群 CSF1 受体（CSF1 receptor，CSF1R）$^+CD14^+CD68^+$淋巴瘤相关髓系单核细胞，可通过前列腺素 E2（prostaglandin E2，PGE2）-EP2/EP4 轴抑制 CAR-T 功能。与这些临床前发现一致，巨噬细胞功能状态可反映接受 CAR-T 治疗患者的结局。在 DLBCL 患者中，相较于完全缓解者，部分缓解患者肿瘤内 M2 巨噬细胞比例显著更高[63]。在 MM 患者中，CAR-T 治疗后疾病进展患者骨髓巨噬细胞比例显著增加，并且表现为促瘤表型，诱导 T 细胞耗竭并通过复杂细胞间通讯支持骨髓瘤细胞存活[40]。巨噬细胞浸润模式同样可影响 CAR-T 疗效。一项研究[64]通过空间分析发现，未达完全缓解的淋巴瘤患者其程序性细胞死亡受体 1（programmed cell death protein 1，PD-1）$^+$ T 细胞与邻近程序性死亡体配体 1（programmed death ligand 1，PD-L1）$^+$巨噬细胞的距离更近。基于以上证据，重编程巨噬细胞的极化状态、恢复其抗肿瘤功能，已成为协同提升CAR-T疗效的重要研究方向。

诸多临床前研究致力于通过靶向 M2 型巨噬细胞，或逆转其极化状态，或将其特异性清除，以增强 CAR-T 疗法的效果。其中，靶向 CSF1/CSF1R 轴是关键策略之一。该轴是促进 M2 极化的核心调控因子；研究表明，CSF1R 抑制剂能够重编程单核巨噬细胞，使其转化为免疫支持性表型[65]，当与 CAR-T

联合使用时展现出协同抗肿瘤效应[62]，鉴于CSF1R 抑制剂已获批上市，该联合策略极具临床转化潜力。Liu 等[66]提出联合阻断 AIM2 炎症小体信号和 α1 肾上腺素能受体（α1-adrenergic receptor，α1-AR）信号可逆转 M2 极化，减少巨噬细胞 IL-1β 的产生，从而增强 CAR-T 的疗效与安全性。Luo 等[67]报道了另一种协同方案：核输出蛋白 1（exportin-1，XPO-1）抑制剂 Selinexor 可抑制 M2 极化，并上调 CAR-T 细胞表面与存活相关的神经生长因子受体（nerve growth factor receptor，NGFR）表达，进而增强其增殖、细胞毒性并延缓耗竭。靶向 M2 巨噬细胞标志物以减轻其对 CAR-T 的免疫抑制也是可行的策略。如利用靶向叶酸受体 β（folate receptor β，FRβ）的 CAR-T 可清除肿瘤微环境中 FRβ$^+$肿瘤相关巨噬细胞，将肿瘤微环境从免疫抑制转化为免疫支持状态。因此，将 FRβ-CAR-T 作为预处理方案，可能有利于后续肿瘤特异性 CAR-T 的治疗[68]。Luo 等[69]则设计了靶向 FRβ 的 Toll 样受体 7（Toll-like receptor 7，TLR7）激动剂（FA-TLR7a）。FA-TLR7a 特异性靶向 FRβ 而被免疫抑制性髓系细胞内化摄取并激活 TLR7 通路，重编程 M2 等免疫抑制细胞为促炎抗瘤表型。FA-TLR7a 与CAR-T 的连用展现出协同抗肿瘤效应。受体酪氨酸激酶 AXL 在 Th2 及 M2 等免疫抑制细胞上高表达，小分子 AXL 抑制剂靶向清除 M2 等免疫抑制细胞并改善 CAR-T 表型，促进其 Th1 极化并减少免疫抑制性 Th2 相关细胞因子（如 IL-4、IL-13、IL-10）的分泌[70]。除了直接靶向 M2 巨噬细胞，另一大策略是解除肿瘤微环境对巨噬细胞吞噬功能的普遍抑制，从而激活其固有的抗肿瘤能力，间接增强 CAR-T 疗效。其中，CD47/SIRPα 轴是最成熟的靶点。CD47 在多种肿瘤细胞中高表达，通过与巨噬细胞表面的 SIRPα 结合传递信号，阻断该轴可恢复巨噬细胞的抗肿瘤活性，已有多种 CD47 阻断抗体进入临床试验[71]。目前 CD47/SIRPα 轴抑制与 CAR-T 联合主要通过 CAR-T 局部递送 CD47 阻断剂来实现，以减轻全身给药的毒副作用并避免靶向非肿瘤细胞的竞争[72-73]。CD24/Siglec-10 轴是另外一个类似通路，Sun 等[59]设计的 CD24/BCMA 双特异性 CAR-T 不仅可通过靶向 CD24 与 BCMA 清除骨髓瘤细胞，还可阻断 CD24/Siglec-10 通路，促进巨噬细胞对骨髓瘤细胞的吞噬。

CAR-巨噬细胞（CAR-marcophage，CAR-M）疗法本身是将 CAR 的精确定向与巨噬细胞的固有抗肿瘤功能相结合的新兴领域[74]。Liu 等[75]发现了 CAR-T 与 CAR-M 之间存在正向反馈循环：CAR-T 释放的促炎细胞因子将 CAR-M 极化为抗瘤 M1 表型，而 CAR-M 激活后表达的共刺激配体反过来增强 CAR-T 活性，表现为两者的协同抗肿瘤作用。

综上所述，靶向巨噬细胞以增强 CAR-T 疗效的策略丰富多样，但大多数仍处于临床前研究阶段，其真正的临床应用潜力有待未来的探索与验证。

3　髓源抑制细胞

髓源抑制细胞（myeloid-derived suppressor cell，MDSC）是在慢性感染或肿瘤等情况下，髓系前体受持续炎症或髓系生长因子刺激，病理性激活的一组未成熟髓系细胞，具有强大的免疫抑制功能。根据其起源，主要分为多形核 MDSC（polymorphonuclear-MDSC，PMN-MDSC）和单核 MDSC（monocytic-MDSC，M-MDSC）两大类[76-77]。在血液肿瘤患者中，MDSC 水平升高与预后不良相关[78-80]。MDSC 可通过表达免疫检查点，分泌抑制性细胞因子，代谢剥夺，释放活性氧（reactive oxygen species，ROS）等方式抑制 T 细胞与 NK 细胞的抗肿瘤活性[76]。CAR-T 细胞的活性与疗效同样受到 MDSC 的抑制。已有多项研究[81-83]报道，高水平 MDSC（特别是 M-MDSC）与 CAR-T 体内扩增不良或疗效不佳相关，提示 MDSC 参与 CAR-T 耐药机制并可作为提升 CAR-T 疗效的联合治疗靶点。为此，研究人员开发了多种策略，主要包括阻断 MDSC 的募集、抑制其功能或直接靶向清除 MDSC。例如，两项研究[84-85]通过不同途径减少了 MDSC 向肿瘤的迁移：其一是联合使用 Olaparib，其二是改造 CAR-T 使其表达 CXCR4 受体。这两种方法都通过减少肿瘤相关成纤维细胞释放的基质细胞衍生因子-1α（stromal cell derived factor-1α，SDF-1α），减少 MDSC 向肿瘤的迁移，从而提升了 CAR-T 在实体瘤中的疗效。全反式维甲酸在小鼠模型中可降低 M-MDSC 水平，并减弱 PMN-MDSC 的免疫抑制作用。与 CAR-T 联合时展现出协同抗

肿瘤疗效[86]。此外,MDSC 表达 TNF 相关凋亡诱导配体受体 2(TNF-related apoptosis-inducing ligand receptor 2,TR2),Nalawade 等[87]设计了靶向 TR2 和肿瘤抗原的双特异性 CAR-T,其能够有效清除肿瘤内部 MDSC,改善肿瘤微环境。MDSC 同样高表达 CD33、CD123 等分子,联合靶向这些抗原的药物或 CAR-T 可能改善单一 CAR-T 的疗效[88-89],但造血干细胞表面同样表达这些抗原[90],需特别注意其可能引发的血液毒性。

4 树突状细胞

树突状细胞(dendritic cell,DC)作为关键的抗原提呈细胞,在激活 T 细胞介导的抗肿瘤免疫中发挥着核心作用。然而,肿瘤微环境中富含的免疫抑制组分会损害 DC 的免疫激活功能,反而使之倾向于促瘤表型[91]。目前已鉴定出 4 种关键 DC 亚群,包括常规 DC(conventional DC,cDC)、浆细胞样 DC(plasmacytoid DC,pDC)和单核细胞来源 DC(monocyte-derived DC,moDC),其中 cDC 又可进一步分为类型一(cDC1)和类型 2(cDC2)[91]。cDC1 具有最强的抗原提呈与 $CD8^+$ T 细胞激活功能,其浸润与肿瘤良好预后相关[92];cDC2 则被认为与启动 $CD4^+$ T细胞抗肿瘤反应相关[93]。pDC 的抗原提呈功能相对较差,主要通过产生 1 型 IFN 参与抗病毒/肿瘤免疫。然而在肿瘤微环境中,pDC 通常被重编程为耐受表型,促进肿瘤免疫逃逸,并且在多种肿瘤中其浸润与预后不良相关[94]。

DC 的类型可能影响其与 CAR-T 细胞的相互作用结果。一方面,CAR-T 细胞释放的 IFN-γ 能够募集 cDC1,并促进其分泌 IL-12;而 IL-12 反过来又能增强 CAR-T 的细胞毒性,从而在两者之间形成一个正向反馈回路[95]。另一项研究[96]也指出 cDC1 对过表达 CD40 配体CAR-T的抗肿瘤活性是必要的。此外,CAR-T疗法也能增强 cDC1 的抗原提呈功能,其富集和功能状态与 CAR-T 的良好疗效相关[97-98]。另一方面,某些 DC 亚型则可能与疗效不佳相关。例如,未达到完全缓解的 MM 患者外周血中 pDC 水平显著升高[42]。Li 等[40]则在 CAR-T治疗后复发的 MM 患者中发现 $ISG15^+$DC 亚群的比例增加。这些证据提示,肿瘤微环境中的 DC 具有高度异质性,不同亚型对 CAR-T 疗效的影响可能截然相反。未来研究有待进一步评估这些 DC 亚群作为预后预测标志物的潜在价值。

近年提出许多靶向 DC 以提升 CAR-T 疗效的策略,如通过基因工程手段使 CAR-T 细胞分泌 IL-7、CCL9、CCL21、X-C 基序趋化因子配体 1(X-C motif chemokine ligand 1,XCL1)、Fms 样酪氨酸激酶 3 配体(Fms-related tyrosine kinase 3 ligand,Flt3L)等因子,可有效增加 DC 在肿瘤中的浸润,进而激活内源性 T 细胞,发挥协同抗肿瘤作用,并且诱导表位扩展,克服 CAR-T 识别抗原有限的局限性[99-103]。另外,有研究通过过继 DC 增强 CAR-T 疗效。Akahori 等[104]设计了识别 WT1235-243/HLA-A*2402 复合物的 CAR-T 细胞,该CAR-T在表达 WT1 的肿瘤模型中显示出疗效,而接种装载 WT1 抗原的 DC 则增强了相应 CAR-T 的扩增和激活,表现为抗肿瘤效应增强。Ghasemi 等[105]改造 DC 祖细胞,使之表达 IL-12 和 Flt3L。这种工程化细胞无需抗原负载即可在体内分化为 cDC1,并通过诱导 IFN-γ 反应发挥抗肿瘤活性。与 CAR-T 联合应用时,它们能通过 IL-12 直接增强 CAR-T 功能,并通过 IFN-γ 激活内源性免疫应答,形成协同抗肿瘤效应。另外,DC 来源的外泌体保留激活 T 细胞的特性,也是有潜力的替代方案[106]。目前在小样本临床试验[107]中初步显示 DC 与CAR-T联合的治疗潜力:8 例复发难治急性 B 淋巴细胞白血病(B-lineage ALL,B-ALL)患者接受 CD19 CAR-T 输注,均达到微小残留病阴性完全缓解,并在中位间隔49 d后接受 DC 注射,DC 使CAR-T再度扩增,CAR-T中位持续时间为 336 d,患者中位无白血病生存期为489 d。

5 小结

CAR-T 细胞疗法代表了过继性细胞疗法的巨大飞跃,但其疗效仍受限于 CAR-T 持久性不足、肿瘤抑制微环境以及毒性反应。本综述阐明,CAR-T 细胞的命运与功能和先天免疫系统进行着持续且复杂的动态对话。先天免疫细胞,如巨噬细胞、NK 细胞和 DC,以及大量的细胞因子网络,在 CAR-T 细胞的激活、扩增、浸润和最终效能中扮演着双重

角色:一方面,先天免疫细胞可以通过协同抗肿瘤效应、提供共刺激信号、重塑免疫抑制微环境来增强 CAR-T 细胞功能;另一方面,它们也能通过抑制性信号、代谢竞争等机制抑制或耗竭 CAR-T 细胞。

值得强调的是,近年来新兴的高分辨率、多维度的生物学系统解析技术为分析 CAR-T 与先天免疫细胞间的复杂互作提供了精准工具。单细胞多组学技术通过在单细胞水平整合基因组、转录组、蛋白质组及表观组的多维度数据,能够精准揭示细胞异质性特征、细胞功能状态的复杂调控网络及动态演化规律[108-109]。就 CAR-T 与先天免疫细胞而言,在单细胞水平上解析 CAR-T 和各类先天免疫细胞的细胞状态谱系及功能重塑过程,有助于识别决定疗效与毒性的关键细胞亚群和调控通路。结合纵向采样,这些技术有望揭示 CAR-T 输注前后免疫微环境的动态重构,为优化患者分层、预测疗效与制定个体化联合方案提供生物学依据。空间转录组学则进一步弥补了传统组学的空间信息缺失[110],有助于揭示 CAR-T、先天免疫细胞与肿瘤细胞之间的空间邻域关系和功能生态位。借助该技术,可以系统分析 M2 型巨噬细胞、MDSC 等免疫抑制群体的空间富集模式,解析其与 CAR-T 浸润深度、效应持久性的空间关联,从而为设计更精准的局部调控策略(如局部药物递送)提供依据。另外,人工智能与机器学习在处理复杂多维组学数据、模拟细胞间相互作用方面展现出巨大潜力[111]。未来可利用人工智能模型整合患者基线特征、肿瘤基因组、免疫微环境图谱及 CAR-T 产品特性,预测患者对 CAR-T 疗法的应答与毒性,并助力设计优化联合治疗策略(如与特定免疫调节剂、靶向药物或工程化免疫细胞的联用),以协同增强 CAR-T 细胞功能、克服微环境抑制,最终实现更持久且更安全的抗肿瘤疗效。

综上所述,先天免疫细胞对 CAR-T 治疗具有显著影响,其作用具有高度的复杂性与双重性。未来研究需进一步阐明不同先天免疫细胞亚群在 CAR-T 治疗过程中的动态变化及其调控网络,并利用单细胞多组学、空间转录组学及人工智能等前沿技术,系统解析 CAR-T 与免疫微环境相互作用的时空特征与分子机制。在此基础上,通过设计联合治疗策略,如靶向抑制性细胞、重塑支持性微环境或工程化改造 CAR-T 以主动调控先天免疫,有望打破当前 CAR-T 疗法的瓶颈,最终实现先天免疫-适应性免疫协同的下一代 CAR-T 疗法。

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