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$CD4^+$ T细胞在结直肠肿瘤中的作用及靶向$CD4^+$ T细胞的抗肿瘤策略研究进展

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摘 要:$CD4^+$ T细胞在结直肠癌免疫微环境中发挥双重调控作用,既可促进抗肿瘤免疫,也可参与免疫抑制,是决定免疫治疗效果的关键因素。本文系统综述了结直肠癌中$CD4^+$ T细胞各亚群(包括Th1、Th2、Th9、Th17、Treg、Tfh)的分化特征、调控机制及其在肿瘤免疫中的复杂功能。Th1和Tfh细胞通过分泌IFN-γ、IL-21等细胞因子,促进$CD8^+$ T细胞和B细胞功能,增强抗肿瘤反应,与患者良好预后及免疫检查点抑制剂敏感性密切相关。而Th2、Th17及Treg细胞在特定微环境中表现出促肿瘤特性,如诱导免疫抑制、促进血管生成和上皮-间质转化,与微卫星稳定(MSS)型结直肠癌患者免疫耐药性相关。本文进一步总结了$CD4^+$ T细胞在免疫检查点阻断、癌症疫苗和CAR-T细胞疗法中的作用机制与临床应用进展。例如,纳武利尤单抗联合伊匹木单抗在微卫星高度不稳定(MSI-H)型CRC中疗效显著;个体化新抗原疫苗与mRNA疫苗展示出激活$CD4^+$ T细胞辅助功能的潜力;在CAR-T细胞疗法中,$CD4^+$ T细胞可增强疗效并延长免疫应答持续时间。尽管取得重要进展,MSS型CRC对免疫治疗响应有限、$CD4^+$ T细胞异质性高、联合疗法的安全性与疗效平衡等问题仍待解决。未来应聚焦于精准调控$CD4^+$ T细胞分化、逆转免疫抵抗、优化工程化T细胞设计,并加强临床转化研究,以实现从“认识微环境”到“重塑微环境”的跨越,为结直肠癌患者提供更有效的免疫治疗策略。

关键词:结直肠癌;$CD4^+$ T细胞;免疫治疗
中图分类号:R730.51;R735 **文献标识码**:A

The role of $CD4^+$ T cells in colorectal tumors and research progress on targeting $CD4^+$ T cells for antitumor strategies

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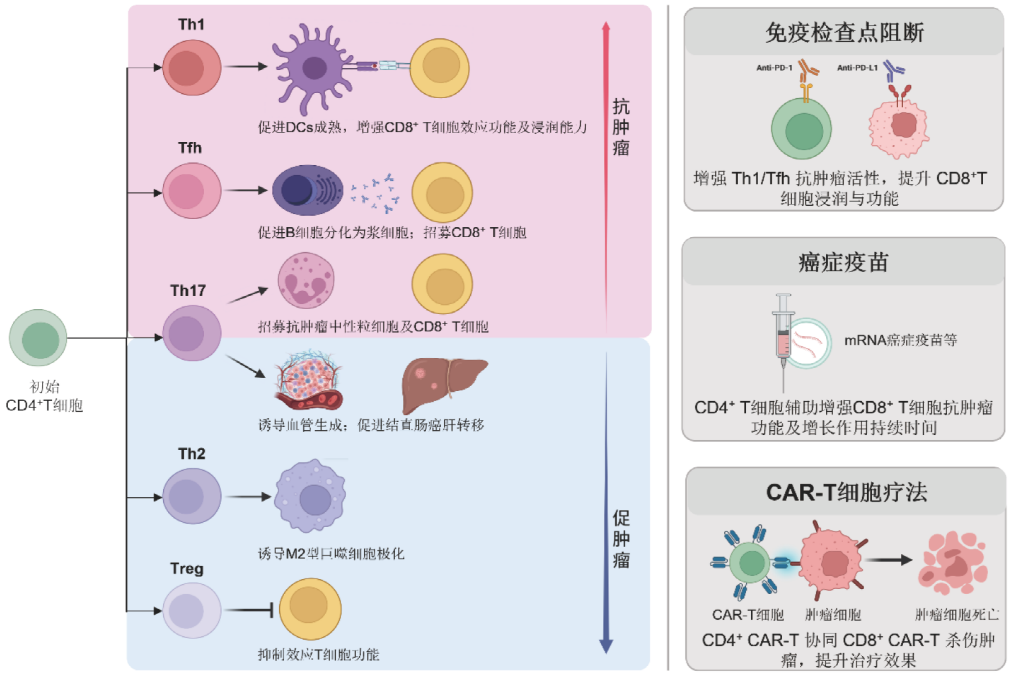
Abstract: $CD4^+$ T cells exert dual regulatory roles in the colorectal cancer (CRC) immune microenvironment, capable of promoting anti-tumor immunity while also contributing to immunosuppression, making them critical determinants of immunotherapy efficacy. This review systematically summarizes the differentiation characteristics, regulatory mechanisms, and complex functions of $CD4^+$ T cell subsets in CRC, including Th1, Th2, Th9, Th17, Treg, and Tfh cells. Th1 and Tfh cells promote $CD8^+$ T cell and B cell functions by secreting cytokines such as IFN-γ and IL-21, thereby enhancing anti-tumor responses, which are closely associated with favorable patient prognosis and sensitivity to immune checkpoint inhibitors. In contrast, Th2, Th17, and Treg cells exhibit pro-tumor properties in specific microenvironments, such as inducing immunosuppression, promoting angiogenesis, and facilitating epithelial-mesenchymal transition, correlating with immune resistance in microsatellite stable (MSS) CRC patients. This review further summarizes the mechanisms and clinical application progress of $CD4^+$ T cells in immune checkpoint blockade, cancer vaccines, and CAR-T cell therapy. For instance, the combination of nivolumab and ipilimumab has shown significant efficacy in MSI-H CRC; personalized neoantigen vaccines and mRNA vaccines demonstrate the potential to activate the helper functions of $CD4^+$ T cells; in CAR-T cell therapy, $CD4^+$ T cells can enhance therapeutic efficacy and prolong the duration of immune responses. Despite important advances, challenges remain, including the limited response of MSS CRC to immunotherapy, the high heterogeneity of $CD4^+$ T cells, and the need to balance safety and efficacy in combination therapies. Future research should focus on precisely regulating $CD4^+$ T cell differentiation, reversing immune resistance, optimizing engineered T cell design, and strengthening clinical translational studies, so as to achieve the transition from ″understanding the microenvironment″ to ″remodeling the microenvironment", ultimately providing more effective immunotherapy strategies for CRC patients.



Key words: colorectal cancer; $CD4^+$ T cells; immunotherapy

结直肠癌(colorectal cancer,CRC)是全球第三大高发恶性肿瘤(发病率9.6%),约占全球每年确诊癌症及癌症相关死亡病例的10%,致死率高居第二(9.3%)[1,2]。尽管手术联合化疗可改善早期患者预后,但晚期CRC的5年生存率仍不足15%[3]。研发新的CRC治疗手段,提升临床治疗效果,是肿瘤治疗领域面临的重大挑战。癌症免疫疗法的出现,如同破晓曙光,不仅为晚期癌症患者带来了新的希望,也推动了整个癌症治疗领域的变革[4],并在2013年被*Science*杂志评选为年度重大突破之首[5]。

癌症免疫疗法的核心在于激活或增强人体的免疫系统,使其能够更有效地识别并消灭肿瘤细胞[4,6]。近年来,基于T细胞的免疫疗法已发展成为肿瘤学中成熟的治疗工具[7]。具体而言,该领域的主要进展包括免疫检查点抑制剂(immunological checkpoint inhibitors,ICIs)的开发和过继细胞疗法(adoptive cell therapy,ACT)的飞速发展。ICI,如抗PD-1/PD-L1单克隆抗体,旨在通过阻断共抑制信号

通路来释放T细胞的活性,从而恢复其抗肿瘤免疫反应[8]。抑制PD-1/PD-L1可以重新激活T细胞的细胞毒能力并诱导肿瘤消退,阻断PD-1/PD-L1通路在临床取得了显著的疗效,而靶向PD-1/PD-L1的抗体也已被批准用于治疗多种癌症[9-12]。ACT,以嵌合抗原受体-T细胞(chimeric antigen receptor T cell,CAR-T)疗法为代表,通过体外基因工程改造患者的T细胞,为其装备嵌合抗原受体,经过体外扩增后,再把这些T细胞重新输回患者体内,达到精准识别并杀伤肿瘤细胞的目的[13-15]。

在早期关于T细胞免疫功能的研究中,大多聚焦于具有直接杀伤肿瘤细胞能力的CD8+ T细胞[16],而现在,越来越多的研究开始重新审视CD4+ T细胞在癌症免疫治疗中的重要性[17-21]。研究表明,CD4+ T细胞通过与共刺激分子的相互作用或分泌细胞因子,为CD8+ T细胞提供关键支持,从而增强其细胞毒性功能和存活时间,并调节肿瘤微环境(tumor microenvironment,TME)[22]。此外,CD4+ T细胞还能通过调节其他免疫细胞亚群而间接增强抗肿瘤免疫反应,例如,它们可以与B细胞相互作用,以促进免疫球蛋白亲和成熟、类别转换重组以及长寿命浆细胞和记忆B细胞的产生[23];与骨髓驻留巨噬细胞相互作用,调节巨噬细胞的极化状态进而引发抗肿瘤反应[24];以及抑制肿瘤组织中血管系统的形成,从而发挥抗肿瘤作用[21]。值得注意的是,细胞毒性CD4+ T细胞已被证实能够通过颗粒酶和穿孔素介导的途径,直接诱导肿瘤细胞的凋亡[25]。但CD4+ T细胞也可能参与形成免疫抑制环境,阻碍抗肿瘤免疫反应的顺利进行[26]。

本文聚焦CD4+ T细胞在CRC中的作用及治疗转化潜力,系统梳理了近年研究进展,剖析CRC免疫微环境中CD4+ T细胞亚群的分化与作用机制,分析其在免疫检查点阻断、癌症疫苗及CAR-T治疗中的调控效应,并探讨靶向策略的挑战与未来方向。

1 CD4+ T细胞在CRC免疫微环境中的复杂调控作用

1.1 肿瘤特异性CD4+ T细胞的激活与分化

成功激活肿瘤相关抗原(tumor-associated antigens,TAAs)特异性CD4+ T细胞,对于体内的抗肿瘤效应至关重要[27–29]。在CRC免疫微环境中,树突状细胞(dendritic cells,DCs)捕获TAAs后,通过MHC-II分子将其呈递给CD4+ T细胞,促使CD4+ T细胞激活并进行克隆增殖和分化,形成不同的CD4+ T细胞亚群[18](表1)。细胞分化的类型在很大程度上依赖于CD4+ T细胞激活期间微环境中占主导地位的细胞因子成分,同时也受到T细胞受体刺激强度以及抗原呈递细胞(antigen-presenting cells,APCs)的类型和功能状态的影响[30,31]。TME中的CD4+ T细胞亚群,包括Th1、Th2、Th17、调节性T细胞(regulatory T cell,Treg)和T滤泡辅助(T follicular helper,Tfh)细胞等,通过不同机制参与免疫微环境复杂调控,对肿瘤免疫微环境重塑发挥重要作用。CD4+ T细胞亚群的特征及其调控作用见图1。

1.2 抗肿瘤型CD4+ T细胞亚群的作用

1.2.1 Th1细胞

Th1细胞的分化由白细胞介素-12(interleukin,IL-12)启动,IL-12与IL-12受体结合后驱动STAT4介导的Th1细胞分化关键转录因子——T-box转录因子(T-box transcription factor,T-bet)表达[32],促进Th1细胞的分化和发育。同时,IFN-γ通过自分泌作用激活STAT1信号通路,增强T-bet基因的表达,从而进一步推动Th1细胞的极化过程[33]。Th1细胞产生的细胞因子,如IFN-γ和IL-2,可促进CD8+ T细胞的免疫反应。除细胞因子外,Th1细胞还通过CD40-CD40L相互作用直接促进DCs的成熟,增强CD8+ T细胞的效应功能及迁移浸润能力[27]。此外,Th1细胞可在TME中表现出细胞毒性特征,靶向释放颗粒酶和穿孔素,直接清除表达MHC II类分子

表1 CD4+ T细胞主要亚群

Table 1 Major subsets of CD4+ T cells

T细胞亚群	极化细胞因子	关键转录因子	效应细胞因子
Th1	IL-12、IFN-γ	T-bet	IFN-γ、TNF-α、IL-2
Th2	IL-4	GATA3	IL-4、IL-5、IL-13
Th9	IL-4、TGF-β	PU.1	IL-9
Th17	IL-6、IL-1β、TGF-β	RORγt	IL-17、IL-22
Treg	TGF-β、IL-2	FOXP3	TGF-β
Tfh	IL-6、IL-21	BCL6	IL-21

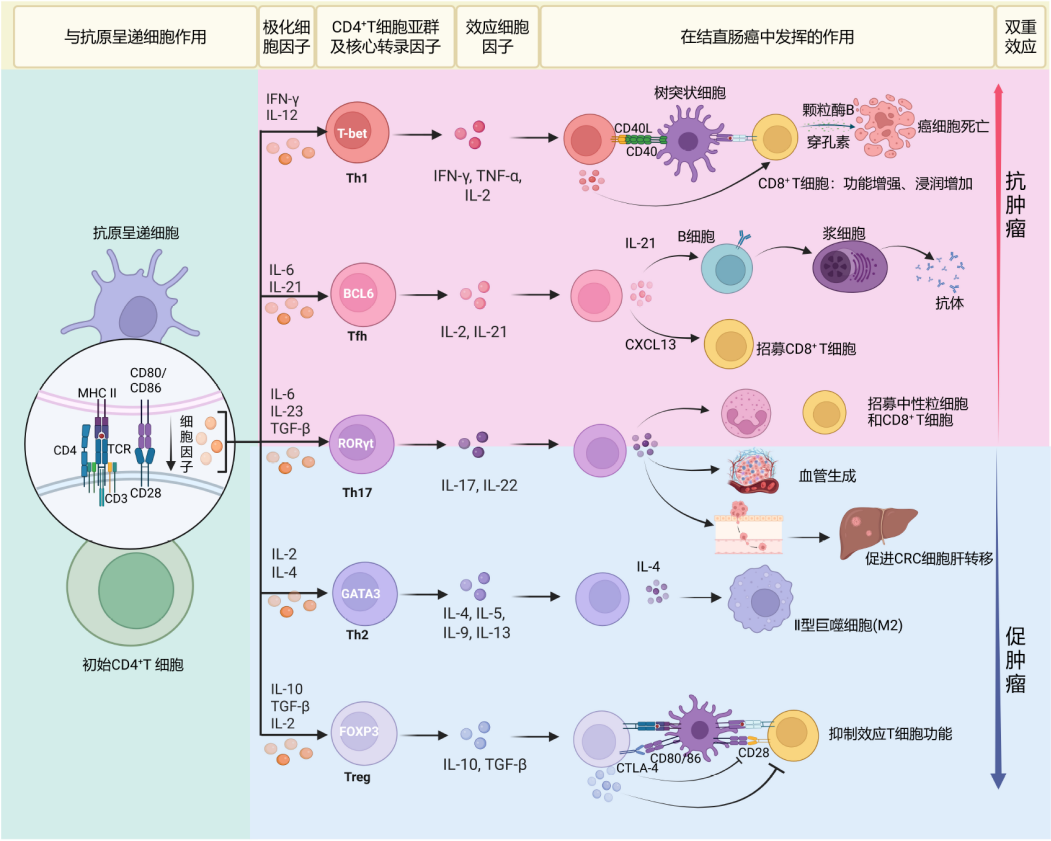


图1 CD4⁺ T细胞亚群的特征及其肿瘤调控作用

的肿瘤细胞[18,34]。据文献报道,Th1细胞在微卫星高度不稳定/错配修复缺陷(microsatellite instability-high/mismatch repair deficient,MSI-H/dMMR)的CRC患者中显著富集,且这些患者通常对免疫检查点抑制剂治疗更为敏感,拥有更为良好的预后,而这可能与Th1细胞强大的抗肿瘤功能密切相关[19,22,35,36]。

1.2.2 滤泡辅助性T细胞

Tfh细胞的分化依赖于IL-21和IL-6这两种细胞因子的协同作用[37],它们通过激活STAT3信号通路对初始CD4⁺ T细胞进行调控,诱导其分化[38,39]。此外,B细胞淋巴瘤6蛋白(B cell lymphoma 6,BCL-6)作为Tfh细胞分化所必需的特异性转录因子,也在其分化过程中发挥关键作用[40-42]。Tfh细胞分泌的IL-21等细胞因子,通过与B细胞表面受体结合,促进B细胞分化为浆细胞并生成抗体[43],这与肿瘤中三级淋巴结构(tertiary lymphoid structures,TLSs)的形成密切相关[34]。研究表明,含有这种激活B细胞的TLSs与CRC患者的低复发风险等良好预后相关[44]。此外,Tfh细胞可以产生招募CD8⁺ T细胞进入TME的趋化因子CXCL13,进而更加有利于抗肿瘤免疫反应的发生[34]。

1.3 促肿瘤型CD4⁺ T细胞亚群的作用

1.3.1 Th2细胞

IL-4通过激活STAT6信号通路促进Th2细胞谱系特异性的转录因子——GATA3的表达,驱动Th2细胞的分化[45,46]。据报道,通过将肿瘤相关巨噬细胞极化为免疫抑制表型(M2),Th2细胞及其产生的IL-4被认为与促肿瘤作用和免疫抑制有关。在结肠癌小鼠模型中,阻断IL-4可减少特定TME中免疫抑制M2表型和髓系来源抑制细胞(myeloid-derived suppressor cells,MDSCs)的生成,并改善肿瘤特异性CD8⁺ T细胞反应[47]。

1.3.2 Th17细胞

Th17细胞的极化是在TGF-β、IL-6以及IL-23等细胞因子刺激下,激活STAT3信号,促进Th17转录调节因子——维甲酸相关孤儿受体γt(retinoic acid-related orphan receptor γt,RORγt)的表达后发生[48]。Th17细胞在微卫星稳定(microsatellite stable,MSS)型患者的肿瘤中富集,这种差异可能与MSS患者对

免疫治疗的耐药性相关[35]。Th17细胞及其衍生的细胞因子会加剧TME中的炎症反应,促进肿瘤生长和免疫抑制[49];另外,Th17细胞已被证明通过诱导血管生成和维持癌细胞存活来促进肿瘤生长[50]。最近的研究表明,Th17细胞通过分泌肿瘤坏死因子样凋亡微弱诱导剂(tumor necrosis factor-like weak inducer of apoptosis,TWEAK),与肿瘤细胞表面的成纤维细胞生长因子诱导早期反应蛋白14(fibroblast growth factor-inducible 14,Fn14)结合,触发上皮-间质转化(epithelial-mesenchymal transition,EMT),促进CRC的肝转移,揭示了Th17细胞在肿瘤进展中的促肿瘤作用[51]。

值得注意的是,Th17细胞的功能并非绝对促肿瘤,其在特定微环境中可表现出抗肿瘤潜力,体现显著的功能异质性。已有研究证实,CRC中的Th17细胞通过分泌IL-8招募抗肿瘤中性粒细胞,分泌CCL5和CCL20及激活内皮细胞间接招募高细胞毒性CD8+ T细胞,进而发挥抗肿瘤作用[52]。

1.3.3 调节性T细胞

Treg是一群具有免疫抑制效应的T细胞,FOXP3的表达是Treg细胞的显著特征[53]。Treg通过分泌免疫抑制性细胞因子,如TGF-β和IL-10,以及表达免疫检查点分子,如CTLA-4和PD-1,抑制效应T细胞功能,削弱其对肿瘤的杀伤能力[54]。据报道,调节性T细胞在CRC的TME中发挥重要的免疫抑制作用,与CRC不良预后成正相关[26]。

2 CD4+ T细胞在CRC T细胞相关免疫治疗中的作用

2.1 接受免疫检查点阻断治疗患者体内的CD4+ T细胞

免疫检查点阻断(immune checkpoint blockade,ICB)治疗通过抑制免疫抑制性受体,如PD-1、CTLA-4的活性,增强T细胞对肿瘤细胞的攻击能力[55]。在ICB治疗过程中,会产生具有传统Th1和Tfh特征的亚群,以及具有细胞毒性特征的Th1亚群,通常与患者的良好预后相关。一方面,这些T细胞亚群可以激活APCs,并为其提供可溶性信号及细胞表面信号,从而激活CD8+细胞毒性T细胞(cytotoxic T lymphocytes,CTLs);另一方面,CD4+ Tfh细胞还可促进B细胞反应,生成抗体后以免疫复合物形成的方式辅助抗原呈递,或靶向癌细胞表面的突变蛋白[34]。

ICB在CRC的应用中已然取得了非常卓著的疗效。最新的CheckMate 8HW研究结果表明,纳武利尤单抗联合伊匹木单抗在治疗MSI-H/dMMR转移性CRC患者时,在安全性可控的条件下,具有显著的有效性(12个月、24个月和36个月的无进展生存率分别为76%、71%和68%;客观缓解率为71%)[56]。然而大多数微卫星稳定/错配修复完整(microsatellite stable/mismatch repair proficient,MSS/pMMR)型CRC患者对免疫检查点抑制剂反应不佳,这可能与MSS/pMMR型CRC的特征,如低突变负荷、免疫原性较弱等因素密切相关[57,58]。因此,使用联合策略来增加抗原载量并迫使免疫系统激活或许是治疗MSS/pMMR型CRC的可行方向。据报道,在MSS/pMMR型CRC患者中,应用PD-1阻断剂联合全程新辅助治疗使33.3%的患者实现了病理完全缓解,48%的患者达到了临床完全缓解,且联合治疗方案未带来显著的额外安全性问题,患者耐受性良好[59]。除PD-1阻断剂联合全程新辅助治疗外,其他联合方案也显示出潜力。在MSS/pMMR晚期CRC中,II期CAPability-01试验(NCT04724239)显示,PD-1单抗信迪利单抗联合HDAC抑制剂西达本胺和抗VEGF贝伐珠单抗的三联方案,将18周无进展生存率提高至64.0%,客观缓解率44.0%,无进展生存期7.3个月,均显著优于双药联合(分别为21.7%、13.0%、1.5个月)[60]。

2.2 接受癌症疫苗治疗患者体内的CD4+ T细胞

癌症疫苗旨在激活针对肿瘤抗原的特异性免疫反应,主要利用TAAs和肿瘤特异性抗原(tumor-specific antigens,TSAs)来激活患者的免疫系统[61],后者可以最大限度地降低严重不良事件的发生风险[62,63]。根据制备方法的不同,癌症疫苗的平台分为四类:细胞疫苗、病毒疫苗、肽疫苗和核酸疫苗[61]。目前,大多数癌症疫苗仍处于临床前研究和临床试验阶段[64]。CD4+ T细胞在疫苗治疗中发挥关键的辅助作用,据报道,能够同时激发CD8+和CD4+ T细胞反应的癌症疫苗通常比单独诱导CD8+ T细胞应答的疫苗具有更好的抗肿瘤效果[65]。这可能有多种原因,包括DCs的激活及其作用时间的增长[66,67]、CD4+ T细胞对CD8+ T细胞抗肿瘤功能的增强[27,68],以及TME中其他细胞成分的变化可能有助于减轻免疫抑制[34]。

癌症疫苗在CRC治疗中较有前景,早在20世纪80年代就已经有科学家使用癌症疫苗进行CRC治疗[69]。GRANITE(GRT-C901/GRT-R902)是Gritstone公司开发的一款个体性新抗原疫苗,通过腺病毒载体(GRT-C901)和自扩增mRNA(GRT-R902)诱导持久的T细胞应答激活,被美国食品和药物管理局授予快速通道资格,用于治疗MSS型CRC。目前,Gritstone公司正在开展一项2/3期研究,以评估GRANITE作为新诊断MSS-CRC患者维持治疗方案的有效性。此外,有研究团队开发了一种新型mRNA癌症疫苗治疗CRC,它通过脂质纳米颗粒递送全反式维甲酸和mRNA刺激肠道中的黏膜免疫反应,且在疫苗激活T细胞的同时诱导肠道归巢受体的高表达,进而使活化的T细胞具有肠道趋向性,大大提高了对CRC的治疗效果[70]。

2.3 接受CAR-T细胞疗法患者体内的$CD4^+$ T细胞

CAR-T细胞疗法是一种过继性细胞免疫疗法,它通过基因工程改造患者自身的T细胞,使其表达嵌合抗原受体,增强其对肿瘤细胞的识别和杀伤能力[71,72]。CAR主要由三个关键功能域组成,即胞外结构域、跨膜结构域和胞内结构域。其中,胞外结构域包含单克隆抗体的单链可变片段,负责识别并结合特定的抗原,同时,该结构域还包含一段铰链区,其主要作用是连接胞外抗原结合域和跨膜结构域以确保CAR在细胞表面的稳定性和功能;跨膜结构域起到锚定CAR到细胞膜的作用;胞内结构域由共刺激结构域和信号转导结构域组成,共刺激结构域能够提供信号以增强T细胞的激活和增殖,而信号转导结构通常为T细胞受体TCR/CD3ζ链,含有免疫受体酪氨酸活化基序(immunoreceptor tyrosine-based activation motifs,ITAMs)从而启动T细胞的免疫反应,促使T细胞发挥抗肿瘤等免疫功能[73]。在抗肿瘤免疫中,$CD8^+$ T细胞被认为是CAR-T疗法的主要效应细胞,而$CD4^+$ T细胞通过多重机制增强治疗效能:一方面,CD40L修饰的CAR-T细胞可增强促炎性Th1细胞因子的增殖和分泌,包括IL-2、IFN-γ等,强化抗肿瘤炎症反应[74];另一方面,$CD4^+$ CAR-T细胞被报道具有较长的体内持续时间,这可能有助于在肿瘤和肿瘤引流淋巴结中维持免疫反应,从而降低肿瘤复发风险[34]。

CAR-T细胞疗法在CRC治疗中处于积极探索阶段。该疗法的关键靶点,包括癌胚抗原(carcinoembryonic antigen,CEA)、鸟苷酸环化酶C(guanylyl cyclase C,GUCY2C或GCC)、间皮素(mesothelin,MSLN)、上皮细胞黏附分子(epithelial cell adhesion molecule,EpCAM)和钙黏蛋白17(cadherin 17,CDH17)等[75]。一项基于CoupledCAR平台技术开发的CD19和GCC双靶点的CAR-T细胞疗法研究,通过靶向CD19激活和扩增CAR-T细胞,随后通过靶向GCC(主要在肠道细胞中表达的受体,在转移性CRC细胞中高度保留,而在其他组织中的表达有限),引导CAR-T细胞特异性地攻击CRC细胞,其临床研究结果显示出良好的疗效和安全性,为晚期CRC患者带来了新的治疗希望[76]。另有靶向CD155的CAR-T细胞的研究显示,该疗法因CD155在消化系统肿瘤中强烈且均匀地表达,但在正常组织中轻度表达,从而对肿瘤细胞具备高效杀伤能力,在消化系统肿瘤(包括CRC)的临床前研究中显示出良好的成效[77]。

3 总结与展望

CRC的免疫微环境极为复杂,其中$CD4^+$ T细胞通过其抗肿瘤与促肿瘤的双重功能,在疾病的发生、发展及治疗过程中起着至关重要的作用。在CRC免疫微环境中,不同$CD4^+$ T细胞亚群展现出多样化的分化特征及作用机制。Th1细胞通过分泌细胞因子如IFN-γ和IL-2,促进$CD8^+$ T细胞的反应,并且可能直接通过颗粒酶、穿孔素等杀伤肿瘤细胞,其在MSI-H/dMMR型CRC患者中显著富集,与患者对免疫检查点抑制剂治疗的敏感性及良好预后密切相关。Tfh细胞则通过产生IL-21等细胞因子,促进B细胞分化为浆细胞和生成抗体,有助于三级淋巴结构的形成,与CRC患者的低复发风险等良好预后相关,同时还能招募$CD8^+$ T细胞进入肿瘤微环境,有利于抗肿瘤免疫反应的发生。Th2细胞通过将肿瘤相关巨噬细胞极化为免疫抑制表型(M2),以及其产生的IL-4等细胞因子,与促肿瘤作用和免疫抑制有关。Th17细胞在MSS型CRC患者的肿瘤中富集,其产生的细胞因子如IL-17、IL-22等,有助于诱导肿瘤微环境中的炎症,促进肿瘤生长和免疫抑制,还能通过诱导血管生成和增加癌细胞存活来促进肿瘤生长,甚至通过分泌TWEAK与肿瘤细胞表面的Fn14受体结合,触发EMT,促进CRC的肝转移;值得注意的是,Th17可以通过分泌细胞因子招募中性粒细胞

及CD8$^+$ T细胞发挥抗肿瘤作用。Treg细胞通过分泌免疫抑制性细胞因子(如TGF-β和IL-10)以及表达免疫检查点分子(如CTLA-4和PD-1),抑制效应T细胞功能,损害其对肿瘤的杀伤作用,与CRC的不良预后成正相关。

在免疫治疗领域,CD4$^+$ T细胞对多种治疗手段的调控效应极为关键。免疫检查点阻断治疗通过抑制免疫抑制性受体的活性,增强T细胞对肿瘤细胞的攻击能力。在治疗MSI-H型转移性CRC患者时,纳武利尤单抗联合伊匹木单抗取得了显著的疗效,产生了具有传统Th1和Tfh特征的亚群,以及具有细胞毒性特征的Th1亚群,与良好预后相关。然而,MSS型CRC患者对免疫检查点抑制剂反应不佳,可能与其低突变负荷、免疫原性较弱等特征密切相关,因此需要探索联合策略来增加抗原载量并激活免疫系统。癌症疫苗作为一种激活针对肿瘤抗原特异性免疫反应的治疗手段,CD4$^+$ T细胞在其治疗中发挥关键的辅助作用,能够同时产生CD8$^+$和CD4$^+$ T细胞反应的癌症疫苗通常比单独诱导CD8$^+$ T细胞应答的疫苗具有更好的抗肿瘤效果。CAR-T细胞疗法通过基因工程改造患者自身的T细胞,增强其对肿瘤细胞的识别和杀伤能力,CD4$^+$ T细胞有助于提高CD8$^+$ T细胞介导的细胞毒性效率,并且CD4$^+$ CAR-T细胞具有较长的体内持续时间,有助于维持免疫反应,限制肿瘤的复发,目前该疗法在CRC治疗中处于积极探索阶段。

尽管在CD4$^+$ T细胞的研究及临床应用方面已取得显著进展,但仍面临诸多挑战。首先,MSS型CRC患者对现有免疫疗法反应有限,亟需开发靶向特定CD4$^+$ T亚群的策略,以逆转免疫抑制微环境,提高治疗效果。其次,CD4$^+$ T细胞的高度异质性导致其功能调控极为复杂,需要借助单细胞测序等先进技术,深入解析亚群间的动态互作网络,以便更精准地调控CD4$^+$ T细胞的功能。此外,联合疗法虽然可能通过多途径协同增强疗效,但如何平衡安全性与有效性是一个亟待解决的问题,需要在临床实践中不断探索和优化联合治疗方案。

未来的研究可聚焦于以下几个方向。一是精准调控CD4$^+$ T细胞分化,利用基因编辑等技术或小分子抑制剂靶向关键转录因子,如T-bet、BCL6、FOXP3等,选择性扩增抗肿瘤亚群并抑制促肿瘤亚群,从而更有效地发挥CD4$^+$ T细胞在抗肿瘤免疫中的作用。例如,利用CRISPR/Cas9敲除IL-2Rα增强子,阻断IL-2信号,促进初始CD4$^+$ T细胞向Th17分化,增强IL-17、IL-22介导的抗肿瘤免疫,或是靶向敲除Usp22、Brd9等FOXP3上游调控基因,降低FOXP3表达,抑制Treg功能,解除免疫抑制[78]。二是克服MSS型CRC的免疫抵抗,探索新抗原疫苗与表观遗传调控联用,或靶向肿瘤微环境中的免疫抑制信号通路,如IL-4/TWEAK通路等,以增强免疫治疗的疗效。三是优化工程化T细胞疗法,设计双靶点CAR-T或整合共刺激分子,增强CD4$^+$ CAR-T细胞的持久性与浸润能力,提高其在实体瘤治疗中的效果。四是加强临床转化验证,通过大规模临床试验评估联合疗法的长期疗效及生物标志物,推动个体化治疗方案的制定,为CRC患者提供更精准、更有效的治疗选择。

总之,CD4$^+$ T细胞作为CRC免疫调控的核心枢纽,其在肿瘤免疫中呈现的复杂调控作用为治疗策略的设计提供了机遇与挑战。未来的研究需紧密结合基础机制探索与技术创新,深入挖掘CD4$^+$ T细胞在CRC免疫微环境中的作用,突破现有治疗的瓶颈,最终实现从“认识微环境”到“重塑微环境”的跨越,为CRC患者带来更高效、更安全的免疫治疗选择,改善患者的预后和生活质量。

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