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Hans汉斯

重塑肿瘤免疫微环境提高免疫治疗效果的研究进展

井水恬[1*]，任晓国[2*]，宫　博[3]，张　翼[4]，高翔鹏[4#]

[1]任丘市人民医院急诊科，河北　任丘
[2]涉县医院肿瘤科二病区，河北　邯郸
[3]保定鼎信知识产权代理有限公司，河北　保定
[4]河北医科大学研究生学院，河北　石家庄

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摘　要

近年来，以免疫检查点抑制剂(Immune Checkpoint Inhibitors, ICIs)为代表的免疫治疗，极大地提高了多种肿瘤的治疗效果，但总体反应率较低。因ICIs的有效性绝对依赖于能够识别和杀伤肿瘤细胞的T淋巴细胞浸润，故ICIs只对“热肿瘤”有效，而对“冷肿瘤”无效。本文通过梳理相关文献，系统、全面地探讨了阻碍T淋巴细胞激活与浸润的常见机制，并总结了重塑肿瘤免疫微环境(Tumor Immune Microenvironment, TIME)提高ICIs治疗效果的方法与研究进展。在免疫治疗时代，如何最大程度地挖掘ICIs的治疗潜力已成为研究热点，值得多角度探讨。

关键词

肿瘤免疫微环境，T淋巴细胞，免疫治疗，免疫检查点抑制剂，冷肿瘤

Research Progress on Reshaping the Tumor Immune Microenvironment to Enhance the Effectiveness of Immunotherapy

Shuitian Jing[1*], Xiaoguo Ren[2*], Bo Gong[3], Yi Zhang[4], Xiangpeng Gao[4#]

[1]Emergency Department, Renqiu City People’s Hospital, Renqiu Hebei
[2]Oncology Ward 2, Shexian Hospital, Handan Hebei
[3]Baoding Dingxin Intellectual Property Agency Co., Ltd., Baoding Hebei

[*]共同第一作者。
[#]通讯作者。

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[4]Graduate School of Hebei Medical University, Shijiazhuang Hebei

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Abstract

In recent years, immune therapy represented by immune checkpoint inhibitors (ICIs) has greatly improved the treatment outcomes for various tumors, but the overall response rate remains low. The effectiveness of ICIs is entirely dependent on the infiltration of T lymphocytes that can recognize and kill tumor cells, which is why ICIs are only effective against "hot tumors" and ineffective against "cold tumors". This article systematically and comprehensively discusses the common mechanisms that hinder T lymphocyte activation and infiltration by reviewing relevant literature, and summarizes methods and research progress in reshaping the tumor immune microenvironment (TIME) to enhance the efficacy of ICIs. In the era of immunotherapy, how to maximize the therapeutic potential of ICIs has become a research hotspot worthy of exploration from multiple perspectives.

Keywords

Tumor Immune Microenvironment, T Lymphocytes, Immunotherapy, Immune Checkpoint Inhibitors, Cold Tumor

1. 前言

因患者个体间及同一个体不同病灶间的 TIME 均具有较大的异质性[1]-[3]，故 ICIs 在实体瘤治疗中的总体有效率仅为 20%~30% [4]。有学者根据免疫细胞在肿瘤组织的浸润情况将肿瘤的免疫表型分为三种：免疫炎症型、免疫排除型和免疫沙漠型[4]，第一种又被称为“热肿瘤”，其特点是高 T 淋巴细胞浸润、干扰素-γ 信号通路激活、PD-L1 高表达和高肿瘤突变负荷(Tumor Mutation Burden, TMB)，后两种又被称为“冷肿瘤”，特点大致与“热肿瘤”相反[5]。“热肿瘤”对 ICIs 治疗敏感，“冷肿瘤”则对 ICIs 治疗无效[6]。嵌合抗原受体 T 细胞(Chimeric Antigen Receptor T cells, CAR-T)疗法在血液系统肿瘤治疗中取得的巨大成功[7] [8]，进一步证明 T 淋巴细胞在抗肿瘤免疫反应中的主导地位[9]，故如何促进 T 淋巴细胞的激活与浸润，即重塑 TIME，以提高 ICIs 的治疗效果已成为肿瘤研究领域的一个共识性思路。本文对阻碍 T 淋巴细胞激活与浸润的常见机制进行了总结，并重点归纳了重塑 TIME 以提高 ICIs 治疗效果的方法与研究进展。本文能够为我国肿瘤免疫学的基础研究提供一定思路，对于临床实践也具有一定的借鉴意义。

2. “冷肿瘤”的形成机制

2.1. 抗原缺乏

肿瘤抗原可分为不伴有基因突变的肿瘤相关抗原(Tumor Associated Antigen, TAA)和由非同义体细胞突变所产生的肿瘤特异性抗原(Tumor Specific Antigen, TSA) [10]。研究表明[11]，具有高 TMB 的肿瘤可

产生更多的 TSA，激活更多 T 淋巴细胞。在许多肿瘤类型中[12]-[14]，高 TMB 与 T 淋巴细胞激活、ICIs 的治疗效果存在显著正相关性，故 TMB 已成为预测 ICIs 治疗效果的指标。

2.2. 抗原加工和呈递障碍

研究表明[15]，肿瘤细胞分泌的 STC1 分子可通过限制病原体相关分子模式和损伤相关分子模式的功能而抑制树突状细胞(Dendritic Cells, DCs)的吞噬作用及 T 淋巴细胞的激活。在人黑色素瘤细胞系中敲除 β2 微球蛋白(β2 Microglobulin, β2M)基因，可导致 MHCI 分子的表达缺失，致使 T 淋巴细胞无法激活[16]。DCs 也是趋化因子配体 9 (CXCL9)和趋化因子配体 10 (CXCL10)的主要分泌细胞[17]，在 T 淋巴细胞的浸润过程中起到重要作用。Fms 样酪氨酸激酶 3 配体(FLT3L)是一种生长因子，与粒细胞－巨噬细胞集落刺激因子(GM-CSF)功能类似，对 DCs 的激活具有重要作用[18]。在一项小鼠肿瘤模型的研究中[19]，FLT3L 可显著增加引流淋巴结(Draining Lymph Nodes, DLNs)中 DCs 的数量和 T 淋巴细胞的浸润。在胰腺导管腺癌中[20]，自噬相关受体 NBR1 可诱导肿瘤细胞表面的 MHC 分子降解，阻碍 T 淋巴细胞激活。

2.3. 肿瘤血管异常与缺氧

研究表明[21] [22]，血管内皮粘附分子、细胞间粘附分子(ICAMs)和血管细胞粘附分子(VCAMs)在 TIME 的形成过程中至关重要。当粘附分子表达下调，会导致血管内皮细胞能量不足，阻碍 T 淋巴细胞浸润[21]。血管内皮生长因子(VEGF)不仅可促进血管内皮细胞增殖，还可以下调 VCAM 的表达，阻碍 T 淋巴细胞浸润[23]。研究证实[22]，当肿瘤血管紧密连接功能下降或周细胞功能出现异常，可导致缺氧与酸中毒，阻碍 T 淋巴细胞激活与浸润。缺氧不仅可促进免疫抑制细胞在 TIME 中聚集[24]，还可以通过上调腺苷(ADO)的表达[25]，抑制 IL-2 分泌和 T 淋巴细胞浸润[26]。由缺氧而激活的 ADO 信号通路在 TIME 中作用广泛，还可以抑制 NK 细胞和 DCs 的功能，并促进骨髓源性抑制细胞(MDSCs)和调节性 T 细胞(Tregs)的聚集[27]。

2.4. 致癌信号通路激活

研究表明[28]，黑色素瘤免疫表型形成与 WNT 通路密切相关。KRAS 突变可通过调节细胞因子和趋化因子的表达而参与免疫逃逸[29]。在一项小鼠肺癌模型研究中[30]，KRAS 和 MYC 的同时激活可上调 CCL9 和 IL-23 的表达，促进基质重编程和血管生成，阻碍 T 淋巴细胞浸润。CDK4/6 和 STAT3 通路的激活与“冷肿瘤”免疫表型形成也密切相关[31] [32]。

2.5. 免疫抑制成分与特殊代谢方式

肿瘤相关成纤维细胞(CAFs)促进肿瘤生长[33] [34]。研究证实[35] [36]，CAFs 分泌 TGFβ，抑制 T 淋巴细胞功能，从而介导免疫逃逸和 ICIs 治疗的耐药性。肿瘤细胞中的吲哚胺 2,3-双加氧酶(IDO)可将色氨酸转化为犬尿氨酸，进而阻碍 T 淋巴细胞激活并促进 Tregs 产生[37]。IDO 还可以通过招募和激活 MDSCs 抑制 T 淋巴细胞浸润[38]。肿瘤相关巨噬细胞(TAMs)可以调节 ECM 和介导 CCL2 和 CCL5 的硝化而阻碍 T 淋巴细胞浸润[39]。集落刺激因子-1 (CSF-1)能够促进髓系细胞向 M2 型巨噬细胞表型分化[40]，表明 CSF-1 在 TIME 中具有抑制作用。在许多肿瘤类型中[37] [41]，糖酵解活性和 T 淋巴细胞浸润显著负相关。CAFs 和 TAMs 也可以导致乳酸堆积，称之为“反瓦氏效应”[41]。研究证实[37]，肿瘤细胞中色氨酸的代谢方式和高胆固醇酯化率均可抑制 T 淋巴细胞受体的聚集及免疫突触形成，阻碍 T 淋巴细胞激活。

3. 重塑 TIME 提高 ICIs 疗效的研究进展

3.1. 促进 T 淋巴细胞激活

3.1.1. 免疫刺激

研究证实[42]，TLR7/8 激动剂可显著激活次级淋巴器官中的 DCs，并上调 MHC-I、CD40 和 CD86 的表达，促进 T 淋巴细胞激活。在一项晚期恶性黑色素瘤的临床试验中[43]，TLR9 激动剂和帕博利珠单抗的联合应用可诱导 I 型 IFN 大量分泌和 T 淋巴细胞浸润增加，显著提高了帕博利珠单抗的治疗效果。STING 信号通路可介导促炎细胞因子和趋化因子的表达增加，从而促进 T 淋巴细胞激活与浸润[44]。CHIN E 等[45]的研究表明，STING 信号通路激动剂 SR-717 不但可以促进 T 淋巴细胞、NK 细胞和 DCs 的激活，还可以诱导 PD-L1 的表达，表明 SR-717 和 ICIs 联合应用可能具有协同作用。在一项 ICIs 耐药的小鼠肿瘤模型研究中，STING 信号通路激动剂 MSA-2 与 ICIs 的联合应用显著增加 T 淋巴细胞浸润[46]，提高了 ICIs 治疗效果，进一步证实两者联合应用具有协同作用。

3.1.2. 溶瘤病毒

溶瘤病毒(Oncolytic Virus, OV)不但可以选择性溶解肿瘤细胞，还可以释放相关抗原激活 T 淋巴细胞，提高 ICIs 治疗效果[47]。OV 可以刺激 CXCL9 和 CXCL10 的大量分泌，并上调选择素和整合素的表达，促进 T 淋巴细胞浸润[48]，此外，OV 能够降解 ECM，消除 T 淋巴细胞浸润的物理屏障，甚至通过不同的方式诱导肿瘤细胞的自噬，从而实现溶瘤效果[49] [50]。据报道[51]，塔利班病毒是首个对黑色素瘤治疗有效的 OV，与帕博利珠单抗联合应用，可以显著增加 IFN-γ 表达和 T 淋巴细胞浸润，从而提高治疗效果[52]。研究证实[53]，柯萨奇病毒和帕博利珠单抗联合应用同样具有协同作用。

3.1.3. 放疗和化疗

以前普遍认为，放疗和化疗是通过直接杀伤肿瘤细胞而发挥作用的。当对局部病灶进行放疗，远处病灶也会随之缩小，这种现象被称为“远隔效应”，表明放疗通过某种方式激活了免疫系统[54]。研究表明[55]，放射线致肿瘤细胞损伤后，活性氧(ROS)和内质网(ER)可参与细胞应激反应，增加免疫原性细胞死亡(Immunogenic Cell Death, ICD)，促进 DCs 激活及 TNF 分泌，从而重塑 TIME。Demaria S 等[56]的研究证实，放疗还能通过诱导肿瘤细胞表达趋化因子促进 T 淋巴细胞浸润。当剂量小于 8~10 Gy 的分段放疗就可以诱导足够的 ICD [56]，故无需为增强抗肿瘤免疫反应而增加放射剂量。许多化疗药物可以增强肿瘤抗原的免疫原性和 T 淋巴细胞浸润[57]。研究证实[58]-[60]，ICD 诱导化疗已经在多种小鼠肿瘤模型中被证实可以重塑 TIME，提高 ICIs 疗效。ICIs 联合化疗具有协同作用已成为共识[61]。

3.1.4. 局部热消融治疗

常用热消融方法包括射频消融(Radiofrequency Ablation, RFA)和高强度聚焦超声消融(High-intensity Focused Ultrasound Ablation, HIFU)。目前，RFA 被广泛应用于多种实体肿瘤的治疗，特别是肝细胞癌。研究显示[62]，RFA 在利用射频交流电转换为热量杀伤消融针周围肿瘤细胞的同时，还能够引起 TSA 释放激活 T 淋巴细胞。HIFU 是一种新型微创消融疗法，精准地将声能传递到肿瘤病灶产生高温，导致细胞凝固性坏死。有趣的是，HIFU 还能通过降解 ECM 促进抗原转移到淋巴结及 T 淋巴细胞激活[63]。RFA 与 HIFU 可重塑 TIME，极有可能与 ICIs 产生协同作用，亟待深入研究。

3.1.5. 肿瘤疫苗

治疗性肿瘤疫苗可以促进特异性 T 淋巴细胞的激活与浸润[64]。普罗文奇是 FDA 批准的第一个治疗性肿瘤疫苗，已被应用于治疗去势抵抗前列腺癌，疗效显著[65]。在一项 Ib 期的临床试验中，个体化新抗原疫苗 NEO-PV-01 与尼鲁单抗的联合使用，显著延长了晚期恶性黑色素瘤、NSCLC 和膀胱癌患者的

无进展生存期[66]，明显提高了尼鲁单抗的治疗效果，说明两者可以产生协同作用。鉴于目前肿瘤疫苗制备成本较高，故在临床中的推广应用受到限制。

3.2. 促进 T 淋巴细胞浸润

3.2.1. 表观遗传修饰类药物

研究证实[67] [68]，表观遗传修饰类药物可以增加包括 CXCL9、CXCXL10 和 CCL5 在内的趋化因子表达，促进 T 淋巴细胞浸润。基于表观遗传修饰的治疗还可以通过增加肿瘤抗原的表达及增强 MHC-I 抗原的加工和呈递过程而促进 T 淋巴细胞浸润[69] [70]。据报道[71]，甲基转移酶抑制剂可上调乳腺癌细胞 MHC-I 的表达，增加 IFN-γ 的分泌，促进 T 淋巴细胞浸润，并与 ICIs 产生协同作用。目前，已有多种表观遗传修饰类药物被 FDA 批准用于肿瘤的临床治疗[72]。此类药物疗效显著，并可与 ICIs 产生协同作用，故发展迅速。

3.2.2. 抑制致癌信号通路

研究表明[73]，在小鼠肿瘤模型中敲除 PAK4 或应用 PAK4 抑制剂可通过 WNT 通路显著增加 T 淋巴细胞浸润，提高 ICIs 治疗效果。内皮细胞 WNT 通路的激活同样可以促进 T 淋巴细胞浸润，与 ICIs 产生协同作用[74]。RAS 突变一直难以成药[75]，但近期的一项研究却有所突破[76]，ARS-1620 作为一种专门靶向 KRAS-G12C 突变体的小分子抑制剂，疗效显著，这很可能是因为同时增强了抗肿瘤免疫反应。在一项小鼠肺癌模型的研究中[77]，MEK 抑制剂与 ICIs 的联合应用显著增加了 T 淋巴细胞浸润，疗效显著。Schaer D 等[78]的研究表明，CDK4/6 抑制剂不仅可以通过抑制 RB-E2F 通路阻碍细胞增殖，还可以促进 T 淋巴细胞浸润，与 ICIs 同时应用产生协同作用。PI3K 抑制剂和 ICIs 的联合应用也可显著促进小鼠肿瘤模型中的 T 淋巴细胞浸润，产生协同作用[79]。

3.2.3. 抗血管生成治疗

促血管生成和抗血管生成信号之间的平衡失调所引起的持续性血管生成是肿瘤特征的标志之一[80]。研究表明[81] [82]，抗血管生成治疗介导的免疫重编程可使肿瘤血管正常化，促进 T 淋巴细胞浸润。贝伐珠单抗是 FDA 批准的第一个抗血管生成药物。在一项转移性肾癌患者的研究中[83]，在贝伐珠单抗和阿替利珠单抗联合应用后 T 淋巴细胞浸润显著增加，可能是由于抗血管治疗介导血管正常化后增强了 T 淋巴细胞的迁移所致。在一项肝细胞癌患者的临床试验中[84]，与索拉非尼治疗的结果相比，阿替利珠单抗联合贝伐珠单抗显著提高了患者的总生存期和无进展生存期。鉴于血管正常化与免疫重编程之间的相关性，抗血管生成治疗联合 ICIs 应用前景广阔。

3.2.4. 抑制 TGFβ 和 CXCR4 功能

在一项小鼠肿瘤模型的研究中[85]，TGFβ 抑制剂和 ICIs 联合应用可显著增加 T 淋巴细胞浸润，降低肿瘤负荷。另有相关报道[86]，Galunisertib 是一种抑制 TGFβ 活性的小分子，在小鼠结直肠癌模型中，可以增加 T 淋巴细胞浸润并提高对 ICIs 治疗的敏感性。研究证实[87]，CXCL12/CXCR4 通路激活可以减少 T 淋巴细胞浸润，并增加免疫抑制性细胞浸润。在一项胰腺导管腺癌模型的研究中[88]，抑制 CXCL12/CXCR4 通路活性可显著促进 T 淋巴细胞浸润，改善预后。ICIs 对胰腺癌通常是无效的，在 COMBAT 试验中，帕博利珠单抗与 CXCR4 抑制剂的联合应用却在转移性胰腺癌中显著增加了 T 淋巴细胞浸润，并减少了 MDSCs 和 Tregs 的数量，明显降低肿瘤负荷[89]。

3.2.5. 纳米药物

纳米药物治疗肿瘤可有三种靶标：肿瘤细胞、TIME 和免疫系统[90]，还可以分为被动靶向和主动靶向，前者是利用实体瘤的高通透性和滞留效应促进纳米药物在肿瘤组织积累的[91]，后者是用靶向配体特

异性识别肿瘤细胞表达的特定受体[92]。研究证实，靶向肿瘤细胞的纳米药物可增加 ICD，从而增强抗肿瘤免疫反应[93] [94]。盐酸多柔比星的聚乙二醇化脂质体 doxil，可增加 ICD，促进 DCs 激活和 T 淋巴细胞浸润并抑制 Tregs 浸润，与 ICIs 产生协同作用[95]。研究报道[96] [97]，当以 TIME 为靶标时，纳米药物不但可以抑制免疫抑制细胞和免疫抑制分子的功能，而且还可以增强效应免疫细胞的活性，与 ICIs 产生协同作用。当靶向免疫系统时，纳米药物旨在增强 DLNs 中的抗原呈递过程和 T 淋巴细胞浸润[98] [99]，理论上与 ICIs 同样可以产生协同作用。

3.2.6. 过继细胞疗法

过继细胞疗法(Adoptive Cell Therapy, ACT)包括肿瘤浸润淋巴细胞(Tumor infiltrating Lymphocyte, TIL)疗法和 CAR-T 疗法两种方式，可以直接增加 T 淋巴细胞数量，增强抗肿瘤免疫反应[100]。由于浸润性 T 淋巴细胞数量较少或 MHC 分子表达下调，TIL 疗法仅适用于包括恶性黑色素瘤在内的少数肿瘤类型[101]。CAR-T 疗法治疗白血病和淋巴瘤在 2017 年获得了 FDA 批准，与 TIL 疗法相比，CAR-T 疗法没有 MHC 分子的限制性，还可以通过添加共刺激分子而进一步增强免疫反应[100]。研究显示[102]，当 CAR-T 细胞表达 IL-7 和 CCL19，可以增加小鼠实体肿瘤组织中 DCs 和 T 淋巴细胞浸润，提高 ICIs 的有效率，而分泌 FLT3L 的 CAR-T 细胞疗法与免疫佐剂的联合应用也可以产生与上述研究类似的结果[19]，说明 CAR-T 疗法可以与免疫佐剂产生协同作用。CAR-T 疗法是利用基因工程使 T 细胞的细胞膜表面表达某种特定肿瘤抗原受体，进而实现对肿瘤细胞的特异性杀伤，而 ICI 则是通过对抑制性共刺激分子的封闭作用保持 T 细胞激活，由于两者作用机制完全不同，故联合应用会产生效果良好的协同作用[103]，值得深入研究。

4. 结论与展望

T 淋巴细胞的激活与浸润对于肿瘤免疫表型的形成至关重要，并与 ICIs 的治疗疗效密切相关。本文总结了抑制 T 淋巴细胞激活和浸润的常见机制，而三级淋巴结构(Tertiary Lymphatic Structure, TLS)和肠道微生物在其中的作用，仍有待于进一步研究[104] [105]。此外，重点论述了促进 T 淋巴细胞激活和浸润的各种治疗方法及研究进展，与 ICIs 联合应用，均可产生协同作用，提高疗效。显然，它们联合应用的最佳剂量和用药顺序仍需深入探索，尽量保证在提高协同作用的同时避免免疫系统过度活化[106]。纳米药物和 ACT 疗法为治愈肿瘤带来了新的希望，相信会在短期内取得突破性进展。在精准医学的时代背景下，随着各个相关学科的迅猛发展及通力合作，我坚信阐明 TIME 的形成机制、研发出更加高效低毒的免疫治疗方法一定会在不久的将来实现。

利益冲突

本文无利益冲突。

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