

· 综述 ·

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局部区域治疗对肝细胞癌免疫微环境的双重调控机制及联合治疗策略

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摘要: 局部区域治疗(LRT), 如经导管动脉化疗栓塞术、经导管动脉放射栓塞术及消融等, 是肝细胞癌的重要治疗手段。近年来多项研究证实其对肿瘤免疫微环境具有双重调节作用; LRT在诱导免疫原性细胞死亡、激活树突状细胞与T细胞免疫并激发全身抗肿瘤应答的同时, 亦可上调腺苷通路、促进髓系细胞触发受体2⁺巨噬细胞聚集并增加免疫抑制因子表达, 进而形成免疫抑制性微环境。目前, LRT与免疫检查点抑制剂的联合治疗前景广阔, 并推动了对相关免疫抑制通路新靶点(如腺苷、髓系细胞触发受体2⁺、白细胞介素6)的探索。本文旨在总结LRT对免疫微环境的双重调控作用, 强调未来需借助多组学技术与临床试验解析其动态变化, 以优化联合策略, 实现个体化精准治疗并改善患者预后。

关键词: 癌, 肝细胞; 肿瘤微环境; 化学栓塞, 治疗性; 消融技术

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The dual regulatory effect of locoregional therapy on the tumor immune microenvironment of hepatocellular carcinoma: Mechanisms and combined treatment strategies

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Abstract: Locoregional therapy (LRT), including transarterial chemoembolization, transarterial radioembolization, and various ablation techniques, is an important treatment method for hepatocellular carcinoma. Many studies in recent years have confirmed that LRT has a dual regulatory effect on tumor immune microenvironment. While LRT induces immunogenic cell death, activates dendritic cell-mediated and T cell-driven immunity, and triggers systemic antitumor responses, it concomitantly upregulates the adenosine signaling pathway, promotes the accumulation of TREM2⁺ macrophages, and enhances the expression of immunosuppressive factors, thereby forming an immunosuppressive microenvironment. At present, the combination of LRT and immune checkpoint inhibitors has shown a promising future and has promoted the exploration of novel targets within treatment-associated immunosuppressive pathways, such as adenosine, TREM2⁺ macrophages, and IL-6. This article summarizes the dual regulatory effect of LRT on immune microenvironment and highlights that multi-omics techniques and clinical trials should be used in the future to decipher its dynamic alterations, in order to optimize combination strategies, realize individualized precise treatment, and improve the prognosis of patients.

Key words: Carcinoma, Hepatocellular; Tumor Microenvironment; Chemoembolization, Therapeutic; Ablation Techniques

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肝细胞癌(hepatocellular carcinoma, HCC)是全球致死率第三的恶性肿瘤^[1],严重威胁人类健康。肿瘤免疫微环境(tumor immune microenvironment, TIME)作为肿瘤学研究的重要前沿,已被证实与HCC的发生、发展及治疗抵抗密切相关^[2]。TIME由淋巴细胞、髓系细胞及基质细胞等构成,其抑制性与刺激性信号间的动态平衡与竞争直接影响HCC的进展、转移及治疗应答,是决定患者预后的关键因素^[3]。

局部区域治疗(locoregional therapy, LRT)贯穿于HCC的多阶段治疗过程,至少50%的HCC患者在病程中接受过此类治疗^[4]。其中,经导管动脉化疗栓塞术(transarterial chemoembolization, TACE)被多项国际指南推荐为巴塞罗那肝癌临床分期B期患者的一线治疗方案^[5],消融治疗则适用于早期HCC,尤其为不适合手术切除的患者提供了根治性选择^[6]。上述治疗既可诱导免疫原性细胞死亡(immunogenic cell death, ICD)、激活全身抗肿瘤免疫,也可能触发负反馈机制加剧免疫抑制,从而限制疗效^[7]。因此,深入研究LRT对TIME的重塑机制,对联合免疫治疗及改善患者预后具有重要意义。

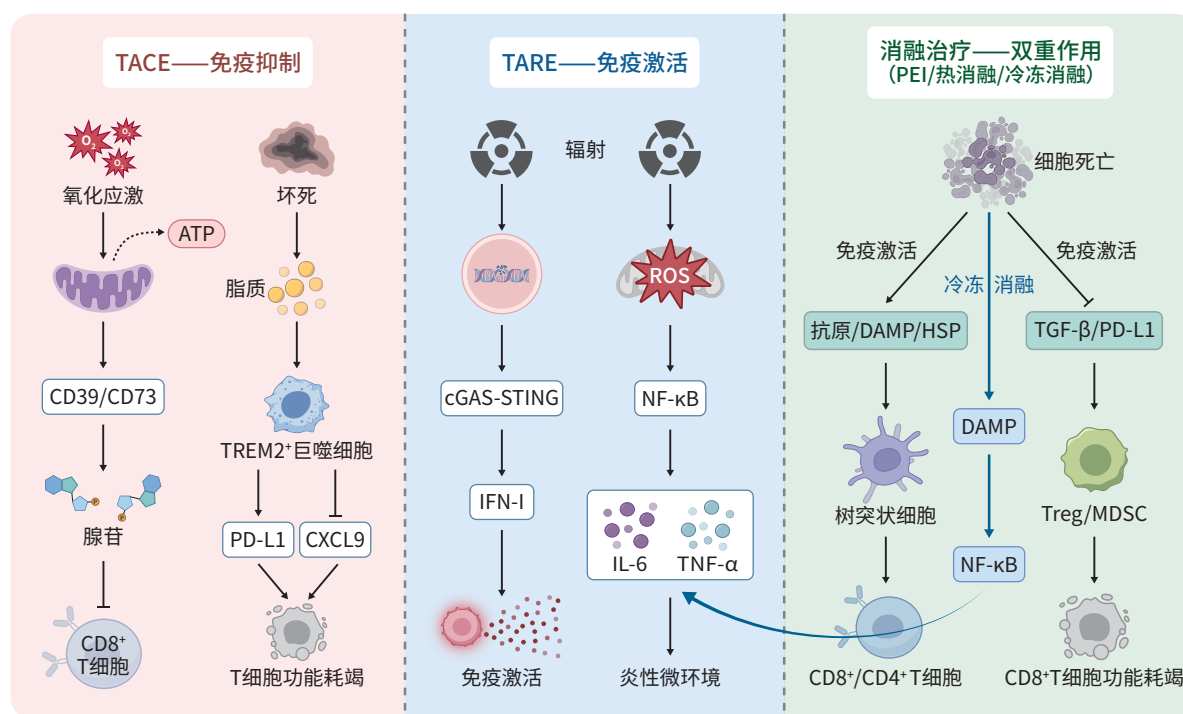
本文系统阐述不同LRT对HCC免疫微环境的复杂调控作用(图1),为临床联合策略提供理论依据。

1 不同类型LRT对TIME调节的机制

1.1 TACE诱导以免疫抑制为主的TIME

TACE通过动脉灌注高浓度化疗药物联合栓塞肿瘤供血动脉,可有效诱导肿瘤缺血坏死。但是,TACE在重塑肿瘤TIME时以免疫抑制为主导,从而促进免疫逃逸,最终引发疾病进展、术后复发及治疗抵抗^[8]。其中,肿瘤细胞缺氧损伤引起细胞膜通透性增加,促使三磷酸腺苷(adenosine triphosphate, ATP)被动扩散至胞外,并依次经CD39和CD73催化生成腺苷^[8]。腺苷是一种强效免疫抑制分子,可以在组织间隙累积并通过结合CD8⁺ T细胞表面的A_{2A}受体,激活胞内环磷酸腺苷-蛋白激酶A信号通路,从而抑制T细胞的增殖、细胞因子产生及杀伤功能^[9]。ATP-腺苷代谢轴在抗原暴露的同时也建立了局部的免疫抑制环境。

除腺苷通路外,巨噬细胞介导的通路是TACE术后免疫抑制的另一核心环节。肿瘤细胞缺氧坏死造成细



注:TACE,经导管动脉化疗栓塞术;TARE,经导管动脉放射栓塞术;PEI,经皮乙醇注射;TREM2,髓系细胞触发受体2;DAMP,损伤相关分子模式;HSP,热休克蛋白;TGF-β,转化生长因子β;PD-L1,程序性细胞死亡配体1;Treg,调节性T细胞;MDSC,髓源性抑制细胞;cGAS-STING,环鸟苷酸-腺苷酸合成酶-干扰素基因刺激蛋白;IFN-I, I型干扰素;NF-κB,核因子κB;IL-6,白细胞介素6;TNF-α,肿瘤坏死因子α;ROS,活性氧;ATP,三磷酸腺苷;CXCL9,趋化因子配体9。

图1 TACE、TARE与消融治疗调控HCC免疫微环境的机制

Figure 1 Mechanisms of TACE, TARE, and ablation therapy in modulating the immune microenvironment of HCC

胞膜破裂,释放大量脂质碎片,后者作为髓系细胞触发受体2(triggering receptor expressed on myeloid cells 2, TREM2)配体被识别,从而招募并促进表达TREM2的肿瘤相关巨噬细胞的存活与增殖,致其在局部显著富集^[10]。TREM2不仅参与调控脂质代谢与吞噬功能,还与免疫抑制性表型密切相关。这类巨噬细胞可通过下调趋化因子配体9削弱CD8⁺T细胞的募集与浸润能力^[11],同时上调半乳糖凝集素1,诱导肿瘤血管内皮细胞高表达程序性细胞死亡配体1(programmed cell death ligand 1, PD-L1),从而在血管周形成免疫抑制性微区域,阻碍T细胞浸润并促进其功能耗竭^[12]。综上,TACE通过激活“ATP-腺苷-CD39/CD73-A₂AR”通路与“脂质-TREM2⁺巨噬细胞-趋化因子配体9/PD-L1”通路,共同介导了局部免疫抑制。因此,靶向上述通路被视为克服联合免疫治疗临床瓶颈的一种关键策略。

1.2 经导管动脉放射栓塞术(transarterial radioembolization, TARE)建立以抗肿瘤免疫为主的TIME TARE通过肝动脉灌注钇-90等放射性微球,利用 β 射线诱导肿瘤DNA断裂进行精准内照射,相较于TACE,其靶向性更强且对正常肝组织损伤更小。TARE主要通过持续低剂量辐射诱导ICD和促炎性微环境重塑,激活抗肿瘤免疫应答,进而能有效抑制肿瘤并增强治疗响应。具体而言,TARE诱导肿瘤细胞发生DNA双链断裂,导致基因组DNA片段异常滞留于细胞质中。这些胞质DNA片段作为危险信号分子,可被模式识别受体环鸟苷酸-腺苷酸合成酶(cyclic GMP-AMP synthase, cGAS)特异性识别^[13]。激活后的cGAS催化三磷酸鸟苷和ATP合成第二信使环鸟苷酸-腺苷酸^[14]。环鸟苷酸-腺苷酸作为胞内信使,与内质网膜上的干扰素基因刺激蛋白(stimulator of interferon genes, STING)结合,该蛋白是天然免疫信号通路的关键接头蛋白,这种结合诱导STING发生构象变化并激活其功能^[15]。活化的STING招募并激活激酶TANK结合激酶1, TANK结合激酶1磷酸化转录因子干扰素调节因子3,磷酸化的干扰素调节因子3形成二聚体并转入细胞核,启动I型干扰素(干扰素 α/β)的转录和分泌,进而激活天然免疫并促进适应性免疫应答^[16]。

辐射产生的活性氧是TARE激活免疫的另一重要机制,其能激活核因子 κ B(nuclear factor kappa B, NF- κ B)信号通路,使其进入细胞核并启动白细胞介素(interleukin, IL)6、IL-12和IL-15等促炎细胞因子的转录^[17]。其中,IL-12可促进CD4⁺T细胞向辅助性T细胞1

型方向分化并增强自然杀伤细胞活性,IL-15支持CD8⁺T细胞和自然杀伤细胞的增殖与存活,IL-6参与T细胞活化和B细胞抗体生成^[18]。上述细胞因子共同塑造了抗肿瘤的免疫微环境。由此可见,TARE通过激活cGAS-STING与NF- κ B两条核心信号通路,协同启动了天然免疫与适应性免疫应答。

1.3 消融治疗对TIME的双重重塑作用

1.3.1 经皮乙醇注射(percutaneous ethanol injection, PEI)通过多靶点激活抗肿瘤免疫并诱导免疫抑制 PEI是一种经典的肿瘤化学消融技术,通过在影像引导下向肿瘤内注入无水乙醇,利用其细胞毒性引起肿瘤细胞凝固性坏死。PEI可诱导ICD,引发肿瘤细胞内质网应激和氧化应激,导致钙网蛋白从内质网转移并暴露于细胞膜表面,同时释放高迁移率族蛋白B1(high mobility group box 1, HMGB1)、ATP等损伤相关分子模式(damage-associated molecular pattern, DAMP)^[19]。钙网蛋白通过与树突状细胞(dendritic cell, DC)表面的I型低密度脂蛋白受体相关蛋白受体结合,增强DC对肿瘤抗原的吞噬能力^[20];HMGB1通过结合Toll样受体4激活DC,促进其成熟和抗原提呈功能;ATP则通过与嘌呤能离子通道型7受体结合,显著增强抗原提呈细胞的活化^[21]。这些信号协同作用,能够有效促进DC对肿瘤抗原的加工和提呈,进而增强CD8⁺T细胞的初次激活和交叉活化,启动特异性抗肿瘤免疫应答^[22]。PEI在激发抗肿瘤免疫应答的同时,亦通过转化生长因子 β 介导的调节性T细胞(regulatory T cell, Treg)分化、缺氧驱动的M2巨噬细胞极化及T细胞耗竭等多重机制,形成免疫抑制微环境^[23]。

1.3.2 热消融技术兼具免疫激活与抑制双重作用 热消融技术在影像引导下将消融电极穿刺入病灶,通过高温使组织发生不可逆凝固性坏死,从而灭活肿瘤。微波消融和射频消融是最常见的热消融技术,其兼具快速消融肿瘤和双向调控TIME的作用。在免疫激活方面,热消融不仅通过诱导肿瘤细胞发生ICD,还释放HMGB1、ATP及钙网蛋白等常规DAMP,尤为关键地释放出大量热休克蛋白(heat shock protein, HSP)^[24]。HSP作为高效的分子伴侣可主动结合肿瘤抗原,形成HSP-抗原肽复合物,该复合物通过DC表面特异性受体(如内皮细胞清道夫受体1、凝集素样氧化型低密度脂蛋白受体1)介导被高效内吞,从而显著增强DC对抗原的摄取、加工与提呈能力^[25]。与此同时, HMGB1和ATP进一步强化DC功能。最终,这些被充分激活的DC迁移至淋巴结,分别通

过主要组织相容性复合体 I 和 II 分子激活 CD8⁺及 CD4⁺ T 细胞,引发强效的抗肿瘤 T 细胞免疫应答^[26]。同时,局部组织释放的肿瘤坏死因子 α 与血管内皮细胞结合,上调黏附分子表达并改变细胞形态,从而提高血管通透性,促进免疫细胞向组织浸润^[27]。但是,热消融同时也会诱发免疫抑制微环境。治疗后肿瘤细胞及髓系细胞常出现 PD-L1 表达上调,Treg 比例升高,髓源性抑制细胞(myeloid-derived suppressor cell, MDSC)扩增并分泌转化生长因子 β 、IL-10 等抑制性因子,进而阻碍效应 T 细胞功能^[28]。研究显示,消融后抗原特异性 T 细胞数量与 MDSC 水平呈负相关,细胞因子谱系向辅助性 T 细胞 2 型偏移,且 Treg/效应性 T 细胞比例失衡,共同加剧免疫耐受状态^[29]。由此可见,热消融兼具激活强效 T 细胞免疫与诱发免疫抑制的双重特性,因此应与免疫疗法联合应用,以协同增强免疫激活效应并削弱免疫抑制,从而实现最佳疗效。

1.3.3 冷冻消融引发强效免疫激活与炎症风险 冷冻消融通过低温冻融循环使肿瘤细胞内外形成冰晶,破坏细胞膜和细胞器,最终导致肿瘤细胞坏死和凋亡。其关键优势在于能最大程度地保留肿瘤抗原的天然构象与免疫原性,从而为激活抗肿瘤免疫提供了独特条件。在免疫激活方面,冷冻过程通过细胞膜破裂可释放大量结构完整的肿瘤相关抗原和 DAMP,进而引发更强烈的抗肿瘤免疫反应^[30]。此外,冷冻消融所营造的免疫微环境不仅能促进 IL-2、干扰素 γ 等促炎性细胞因子的释放,还能有效招募免疫细胞向肿瘤组织浸润,最终产生更显著的远隔效应^[31]。然而,冷冻消融还可诱导免疫抑制和过度炎症反应。治疗过程中通过释放 DAMP 激活 NF- κ B 和促分裂原活化的蛋白质激酶信号通路,促进 IL-6、IL-1 β 和肿瘤坏死因子 α 等促炎因子的产生^[32]。大量产生的炎症因子形成协同放大的细胞因子网络,严重时可诱发细胞因子风暴^[33],表现为高热、低血压及多器官功能障碍。同时,该过程还能通过招募 MDSC 或 Treg 以及上调 PD-L1 等免疫检查点分子,形成免疫抑制性微环境。综上所述,冷冻消融在通过释放完整抗原和 DAMP 以激活强效抗肿瘤免疫的同时,也通过 IL-6 等因子诱发过度炎症及免疫抑制。因此,在联合免疫治疗中,监测 IL-6 与管控细胞因子风暴是实现安全与疗效的关键。

2 临床转化:联合治疗策略与未来展望

2.1 LRT 联合免疫检查点抑制剂 基于免疫联合局部治疗的策略已成为中晚期 HCC 系统治疗的重要方向。

多项 II/III 期临床试验证实,TACE 联合 PD-1/PD-L1 抑制剂(如帕博利珠单抗、阿替利珠单抗)可显著提高患者的客观缓解率(objective response rate, ORR),延长无进展生存期^[34]。例如,一项针对不可切除 HCC 患者的 II 期研究显示,TACE 联合帕博利珠单抗治疗的 ORR 达 46.8%,显著高于传统 TACE 单药的 33.3%^[35]。其协同机制主要源于 TACE 诱导肿瘤抗原释放与免疫检查点抑制剂解除 T 细胞免疫抑制的双重效应,尤其在 TACE 治疗后出现 PD-L1 上调的患者中获益更为显著^[36]。类似地,热消融联合免疫检查点抑制剂也展现出协同增强系统性免疫应答的潜力。一项概念验证研究证明,射频消融与纳武利尤单抗联合治疗后,患者外周血中抗原特异性 T 细胞比例显著升高,远端非消融病灶的控制率也明显提升,提示局部消融可能促进全身抗肿瘤免疫效应的激活^[37]。综上所述,TACE 或热消融与免疫检查点抑制剂的联合应用,为中晚期 HCC 患者提供了具有前景的疗效与可靠的安全性。

2.2 LRT 联合抗血管生成治疗 抗血管生成药物(如贝伐珠单抗、阿帕替尼)可有效逆转血管内皮生长因子介导的免疫抑制微环境,构成了免疫治疗联合抗血管生成这一 HCC 关键治疗策略的基础。IMbrave150 研究确立了“阿替利珠单抗+贝伐珠单抗”(T+A 方案)在不可切除 HCC 一线治疗中的标准地位^[38]。近期有研究进一步探索了 T+A 方案与 TACE 的联合应用,EMERALD-1 研究证实 TACE 联合度伐利尤单抗显著改善无进展生存期^[38];TALENTACE 研究显示 TACE 联合多纳非尼显著提高 ORR^[39];而 LEAP-012 研究(TACE+仑伐替尼+帕博利珠单抗)则未达终点^[40]。综上,抗血管生成药物通过调节 TIME,与免疫治疗及 TACE 产生协同作用,为中晚期 HCC 患者提供了增效甚至根治的可能。

2.3 LRT 联合靶向 TIME 新策略 LRT 后常激活多条免疫抑制通路,目前针对这些通路的靶向干预策略已在临床前及临床研究中取得进展。在腺苷通路方面,CD39/CD73 小分子抑制剂或 A₂A 受体拮抗剂(如 ciforadenant)与 TACE 或免疫检查点抑制剂联用的早期临床试验显示出积极结果,能显著降低外周免疫抑制细胞比例并增强 CD8⁺T 细胞功能^[41]。针对 TACE 术后富集的 TREM2⁺巨噬细胞,抗 TREM2 单抗(如 PY314)可有效阻断其免疫抑制功能,临床前研究证实其与 PD-1 抑制剂具有协同抗肿瘤作用^[42]。对于消融治疗后 IL-6 等细胞因子水平升高的情况,IL-6 受体抑制剂(如托珠单抗)可用于缓解过度炎症状态并减轻免疫抑制,尤其适用于细胞因子风

暴高风险患者^[43]。这些靶向策略为逆转局部治疗后的免疫抑制提供了新的治疗方向。

3 小结与展望

本文主要探讨了TACE、TARE及多种消融技术对TIME的复杂调控作用,并揭示了其与免疫治疗及抗血管治疗联合应用的潜力。然而,对于肝动脉灌注化疗术、不可逆电穿孔术及放射性粒子植入术等其他重要的LRT手段,其在TIME中的特异性调控机制仍有待未来研究进一步阐明。目前面临的主要挑战包括,如何建立生物标志物体系以筛选适宜的患者,确定联合治疗的最佳时机与顺序,利用PD-L1表达,循环肿瘤基因清除率等指标评估疗效,以及管理联合治疗可能增加的毒副作用。

为应对这些挑战,目前单细胞测序与空间多组学等技术已应用于TACE研究,解析了治疗前后免疫细胞亚群的动态转变,并初步构建了免疫抑制微环境的分子图谱^[44]。在此基础上,未来应积极推动大样本、前瞻性临床研究,以获取高级别循证医学证据,为局部治疗与免疫治疗的精准、个体化联合奠定基础,最终进一步提升HCC患者的生存获益。

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