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综 述

巨噬细胞 M1/M2 型极化在结直肠癌肝转移中的作用机制与研究进展

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【摘 要】 肿瘤相关巨噬细胞的 M1/M2 型极化失衡是结直肠癌肝转移的核心免疫驱动力。M1 型由干扰素- γ /脂多糖诱导, 高表达主要组织相容性复合体 II 类分子并产生活性氧杀伤癌细胞; M2 型经白介素-4(IL-4)/IL-13 极化, 通过 IL-10、转化生长因子- β 及血管内皮生长因子主导免疫抑制与血管生成。肝转移灶中 M2 型占优, 借预转移微环境塑造和免疫抑制推进转移。非编码 RNA、m6A 修饰、琥珀酸/HIF-1 α 轴及 IDO1-犬尿氨酸-AhR 通路调控极化方向; 肠道菌群经“肠-肝轴”远程影响极化。外泌体 CD163/CD206 联合血清 miR-146a-5p 与 miR-21-5p 构成“M2 极化评分”可预测肝转移风险。CSF-1R 抑制剂、CD40 激动剂及 STAT3/PI3K γ 抑制剂等重编程巨噬细胞, 与免疫检查点抑制剂联用可减轻肝转移负荷。当前挑战为标志物标准化与靶向转化, 需多组学共识分型推进个体化免疫治疗。文章系统阐述 M1/M2 型极化在 CRC 肝转移中的双向调控机制及进展。

【关键词】 结直肠癌; 肝转移; 肿瘤相关巨噬细胞; M1/M2 极化; 免疫微环境; 作用机制; 再极化治疗

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Role mechanism and research progress of macrophage M1/M2 polarization in liver metastasis of colorectal cancer

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【Abstract】 The M1/M2 polarization imbalance of tumor-associated macrophages represents the core immunological driver of colorectal cancer liver metastasis. M1 macrophages, induced by interferon- γ /lipopolysaccharide, highly express major histocompatibility complex class II molecules and produce reactive oxygen species to kill tumor cells; M2 macrophages are polarized by interleukin-4 (IL-4)/IL-13 and dominate immune suppression and angiogenesis through IL-10, transforming growth factor- β , and vascular endothelial growth factor. In liver metastatic lesions, M2 macrophages predominate, promoting metastasis via pre-metastatic niche shaping and immune suppression. Non-coding RNAs, m6A modification, the succinate/HIF-1 α axis, and the IDO1-kynurenine-AhR pathway regulate the polarization direction; the gut microbiota remotely influences polarization through the “gut-liver axis”. An “M2 polarization score” composed of exosomal CD163/CD206 combined with serum miR-146a-5p and miR-21-5p can predict the risk of liver metastasis. Therapeutic strategies such as CSF-1R inhibitors, CD40 agonists, and STAT3/PI3K γ inhibitors reprogram macrophages, and their combination with immune checkpoint inhibitors significantly reduces liver metastatic burden. Current challenges focus on biomarker standardization and targeted therapeutic translation, necessitating multi-omics consensus subtyping to advance personalized immunotherapy.

【Key words】 Colorectal cancer; Liver metastasis; Tumor-associated macrophages; M1/M2 polarization; Immune microenvironment; Mechanism; Repolarization therapy

肝转移是结直肠癌(colorectal cancer, CRC)患者首要死因, 约 25% 患者初诊即存在同时性肝转移, 另有 50% 出现异时性肝转移^[1]。肿瘤微环境中, 肿瘤相关巨噬细胞(tumor-associated macrophages, TAMs)浸润丰度高、可塑性强, 其 M1/M2 极化方向深刻影响转移进程^[2]。M1 型由干扰素 γ (IFN- γ)/脂多糖

(LPS) 驱动, 呈递抗原并释放活性氧(ROS)杀伤癌细胞; M2 型由白介素 4(IL-4)/IL-13 诱导, 高表达 CD163、CD206, 主导免疫抑制与组织重塑^[3]。肝转移灶内 M2 型 TAMs 占优, 与高转移负荷、化疗耐药及早期复发密切相关^[4]。单细胞与空间转录组学揭示, 分泌型磷蛋白 1(secreted phosphoprotein 1, SPP1)⁺巨噬

细胞富集于缺氧基质界面,补体 C1q C 链 (complement C1q C chain, C1QC)⁺ 巨噬细胞居于免疫浸润区,叶酸受体 2 (folate receptor 2, FOLR2)⁺ 组织驻留巨噬细胞则与 CD8⁺ T 细胞形成抗肿瘤单元,而髓系细胞触发受体 2 (triggering receptor expressed on myeloid cells 2, TREM2⁺) 脂质相关巨噬细胞呈 M2 样免疫抑制特征,更新了传统 M1/M2 二元极化认知^[5]。本文系统阐述 M1/M2 型极化在 CRC 肝转移中的双向调控机制及研究进展。

1 巨噬细胞 M1/M2 型极化的基础理论

巨噬细胞来源多样,组织驻留巨噬细胞如库普弗细胞 (Kupffer cells, KCs) 源于胚胎前体,而在炎症反应及肿瘤中, Ly6C 高表达单核细胞经 CCL2-CCR2 轴大量募集并分化为巨噬细胞^[6]。极化并非二元切换,而是在病原相关分子模式、损伤相关分子模式及微环境信号协同下呈现连续功能谱系^[7]。经典活化巨噬细胞 (classical activated macrophages, M1) 由 LPS 联合 IFN- γ 触发,替代活化巨噬细胞 (alternatively activated macrophages, M2) 由 IL-4/IL-13 介导,且极化状态可随微环境动态逆转^[8]。

M1 型高表达 CD80、CD86、主要组织相容复合体 II (MHC-II), 分泌肿瘤坏死因子- α (TNF- α)、IL-12 及诱导型一氧化氮合酶 (inducible nitric oxide synthase, iNOS) 产生一氧化氮 (NO), 执行杀伤癌细胞和 Th1 型免疫应答^[9]。M2 型特征性表达 CD163、CD206、Arg-1, 分泌 IL-10、TGF- β 、VEGF, 参与免疫抑制、组织重塑和血管生成; 可分为 M2a、M2b、M2c 等功能亚群^[10]。Ricketts 等^[11]指出巨噬细胞呈从 M1 到 M2 的连续活化状态谱系, TAMs 通常被推向 M2 表型, 但极少是纯粹终末状态。

极化调控涉及信号、转录与代谢多层次: JAK-STAT 通路居中枢, IFN- γ /LPS 激活 STAT1 驱动 M1, IL-4/IL-13 激活 STAT6 驱动 M2; NF- κ B/IRF5 协同 M1 极化, PI3K/Akt 促进 M2 转化^[12]。转录网络分别以 IRF5/STAT1 和 STAT6/PPAR γ /KLF4 为核心^[13]。代谢上, M1 依赖糖酵解致琥珀酸蓄积稳定 HIF-1 α ; M2 以氧化磷酸化和脂肪酸氧化供能^[14]。缺氧、乳酸及 CSF-1 等微环境因子不断塑造极化方向。

2 结直肠癌肝转移微环境中 M1/M2 型巨噬细胞的分布特征及核心作用机制

原发灶侵袭前沿以 CD163⁺ M2 为主, iNOS⁺ M1 多聚集于坏死区周边。肝转移灶极化更趋极端: 正常 KCs 虽生理性表达 M2 相关分子, 但肿瘤诱导的病理性 M2 活化截然不同^[15]。肝转移瘤内 M2 标志物表达强度与密度均超匹配原发灶, M1/M2 比值显著倒置^[16]。单细胞测序发现特有的 SPP1⁺ TAMs 亚群, 高表达血管生成与基质重塑基因。空间分布上, M2 型 TAMs 紧密包绕肿瘤巢并沿新生血管排列^[17]。

M2 高浸润密度与转移灶数目增多、更高 TNM 分期及同时性肝转移呈正相关, Xue 等^[18]基于 209 例样本的 Cox 多因素分析证实, CD163⁺ TAM 高浸润是总生存率的独立不良预后因素。M1/M2 比值较单一标志物可提供更精准的预后分层^[19]。该失衡不仅是病理特征, 更是驱动转移的功能性动力。

2.1 M1 型巨噬细胞抑制肝转移的机制 M1 型巨噬细胞在结直肠癌肝转移的多个环节发挥抑癌功能, 构筑机体抗转移免疫

的关键防线。在免疫监视层面, M1 型巨噬细胞凭借高表达 MHC-II 和共刺激分子有效呈递抗原, 激活 CD4⁺ 和 CD8⁺ T 细胞; 同时分泌 IL-12 和 TNF- α , 协同增强 NK 细胞和细胞毒性 T 细胞 (CTL) 的杀伤活性, 促进穿孔素与颗粒酶 B 的释放, 清除经门静脉入肝的循环肿瘤细胞^[20]。效应分子层面, iNOS 催化生成的高浓度 NO 可引起肿瘤细胞 DNA 损伤和线粒体功能障碍, 触发 Caspase 依赖性凋亡; 呼吸爆发产生的 ROS 以氧化应激直接破坏肿瘤细胞膜^[21]。抗血管生成层面, M1 来源的 CXCL9、CXCL10 等趋化因子在募集效应淋巴细胞之外, 还能上调血管抑制因子 (如内皮抑素), 迫使微小转移灶长期处于休眠状态^[22]。在抑制侵袭转移层面, M1 分泌的 TNF- α 可下调 Snail、Twist 等上皮-间质转化 (EMT) 转录因子, 稳定上皮钙黏蛋白, 从而遏制肿瘤细胞的侵袭与播散能力^[23]。转移早期阶段, 维持 M1 极化微环境对清除循环肿瘤细胞、阻止肝内定植至关重要。

2.2 M2 型巨噬细胞促进肝转移的机制 M2 是驱动肝转移级联的核心执行者。在预转移微环境层面, 原发灶来源细胞外囊泡激活 KCs 并向 M2 样转化; M2 分泌基质金属蛋白酶降解肝窦基底膜, TGF- β 诱导肝窦毛细血管瘤化; 分泌纤维连接蛋白和骨桥蛋白促进肿瘤细胞锚定^[24]。在侵袭转移层面, M2 是 TGF- β 、表皮生长因子 (epidermal growth factor, EGF)、肝细胞生长因子 (hepatocyte growth factor, HGF) 等 EMT 诱导因子的主要来源, 激活 Smad/MAPK 通路上调 Snail 等转录因子, 赋予肿瘤细胞高侵袭表型^[25]。在血管生成层面, M2 大量分泌血管内皮生长因子-A (VEGF-A)、血小板源性生长因子-BB (platelet derived growth factor-BB, PDGF-BB) 等诱导病理性血管形成, 并参与血管拟态构建。在免疫抑制层面, M2 通过 IL-10/TGF- β 阻断树突状细胞成熟, Arg-1 消耗精氨酸致 T 细胞活化缺陷, 招募 Treg 和 MDSC, 并上调 PD-L1 诱导 T 细胞凋亡^[26]。在定植增殖层面, M2 与肿瘤细胞通过 CSF-1/EGF 等形成双向旁分泌环路, 激活 PI3K/Akt 和 MAPK 通路加速克隆扩张; 骨桥蛋白增强黏附和存活信号, 抑制失巢凋亡^[27]。KRAS 突变肿瘤细胞通过分泌粒细胞-巨噬细胞集落刺激因子 (granulocyte-macrophage colony stimulating factor, GM-CSF)、CCL2 选择性驱动 M2 样 TAMs 扩增, BRAF 突变依赖 CSF-1 信号重编程巨噬细胞, APC 缺失经 Wnt/ β -catenin 强化 M2 偏倚, 构成了肿瘤分子分型驱动的极化异质性基础。

2.3 M1/M2 型极化动态平衡对肝转移的双向调控作用 结直肠癌肝转移的发生与否, 在免疫层面取决于 M1 型抗肿瘤效应与 M2 型促转移效应之间的动态平衡与博弈。在肿瘤初期, 原发灶局部产生的 IFN- γ 、损伤相关分子模式 (damage associated molecular pattern, DAMPs) 及肠道菌群产物 LPS 等信号驱动浸润巨噬细胞向 M1 方向极化, 此阶段 M1 主导的免疫监视可有效清除大部分入血的循环肿瘤细胞, 肝脏微环境中 M1 型的 KCs 通过主动识别并捕获血管内循环肿瘤细胞, 并向 CD8⁺ T 细胞进行抗原交叉呈递, 从而维持对肝内微转移灶的免疫警觉与抑制状态^[28]。肿瘤进展中 M1/M2 平衡逐渐倾斜: CSF-1、乳酸、CCL2 募集单核细胞并诱导 M2 分化; 缺氧/HIF-1 α 上调 Arg-1 与 VEGF, 驱动 M1 $\rightarrow$ M2 漂移; 凋亡肿瘤细胞磷脂酰丝氨酸经

TAM/Tyro3 信号促使 M2 型极化^[29]。关键转折在微转移灶(<1 mm³)建立功能性血供后,M1 主导的免疫清除被 M2 正反馈取代,M1/M2 比值不可逆倒置,标志由免疫清除转入逃逸与显性进展^[30]。常微分方程模型定量刻画 IL-10/CSF-1 正反馈与 IFN- γ /IL-12 负反馈的非线性,揭示 M1/M2“双稳态”——微小扰动即可触发相变,为干预时间窗提供理论支撑^[31]。Li 等^[32]指出,M2 占优后肝转移灶滑向免疫豁免与快速进展期,M2 信号构成自我强化的恶性环路。因此,阻断 M1→M2 漂移的关键分子开关,恢复动态平衡,是巨噬细胞靶向抗肝转移治疗的核心策略。

3 巨噬细胞 M1/M2 型极化在结直肠癌肝转移中的最新研究进展

3.1 关键调控分子与新信号通路 非编码 RNA 调控巨噬细胞极化与肝转移的关系备受关注。miR-155 靶向 SOCS1 解除 STAT1 负调控,驱动 M1 型极化并阻滞肝转移灶形成^[33];miR-21 则活化 PI3K/Akt 通路,促进 M2 型极化,其在肝转移 TAMs 中的表达较原发灶明显升高^[34]。长链非编码 RNA 方面,lncRNA MM2P 作为 M2 型极化的上游驱动因子,通过调控 STAT6 磷酸化维持 M2 转录程序^[35]。代谢层面,肿瘤来源的琥珀酸经 SUCNR1 激活 HIF-1 α 以稳定 IL-1 β ,但在慢性缺氧条件下,持续琥珀酸信号又通过 HIF-1 α 启动 M2 基因程序,促使长期 M2 偏倚;IDO1 在 M2 型 TAMs 中高表达,其产物犬尿氨酸经 AhR 推动 Treg 扩增与免疫抑制^[36]。m6A 修饰层面,METTL3 介导的 m6A 加速 JAK1 mRNA 降解,削弱 STAT1 信号从而抑制 M1 极化;FTO 去甲基化酶则稳定 STAT3 转录本,驱动 M2 分化^[37]。代谢检查点 mTORC1 借 HIF-1 α 与糖酵解推动 M1,mTORC2 经 AKT 促进 M2,二者平衡决定极化方向,构成潜在可干预节点。

3.2 肠道菌群介导巨噬细胞极化与肝转移 “肠-肝轴”在巨噬细胞极化与结直肠癌肝转移中的作用已成为研究热点。Zheng 等^[38]研究表明,具核梭杆菌感染会导致肿瘤部位 TAMs 浸润增加,促进 M2 型极化并加速 CRC 进展,且通过 TLR4/NF- κ B 通路促进 M2 型巨噬细胞极化;同时具核梭杆菌还可与巨噬细胞等免疫细胞结合,触发肠道黏膜免疫抑制,为 CRC 细胞生存创造有利微环境^[39]。脆弱拟杆菌可通过其毒素或其他代谢产物,营造促炎和免疫抑制的微环境,间接促进巨噬细胞的 M2 样极化,从而可能加速肝转移灶生长^[40]。在菌群代谢产物方面,短链脂肪酸(short-chain fatty acids,SCFAs)中的丁酸被证实通过抑制 HDAC 活性、增强组蛋白 H3K27 乙酰化,重塑巨噬细胞染色质可及性,恢复促炎因子的转录活性和 M1 表型;而菌群失调导致的丁酸减少则解除了对 M2 型极化的抑制。次级胆汁酸脱氧胆酸(deoxycholic acid,DCA)通过激活巨噬细胞 G 蛋白偶联胆汁酸受体 1(G protein-coupled receptor for bile acids,TGR5)受体促进 M2 型极化,而另一种次级胆汁酸石胆酸(lithocholic acid,LCA)则可拮抗此效应,提示胆汁酸代谢谱的干预可调节肝脏免疫微环境^[41]。此外,广谱抗生素预处理清除肠道菌群后,肝转移灶 M2 型 TAMs 比例下降,进一步证实了菌群对肝内巨噬细胞极化的持续远程调控作用^[42]。

3.3 靶向巨噬细胞极化的诊疗标志物与治疗策略 在液体活检领域,循环外泌体表面 CD163 与 CD206 可区分健康个体、CRC 原发及肝转移患者,其内含的 miR-21-5p 和 miR-146a-5p 联合血清 sCD163、CCL2 所构建的“M2 极化评分”可独立预测肝转移风险与术后复发^[43]。血清 sCD163、sCD206 及 IL-10、CCL2 等 M2 标志物水平与转移负荷呈正相关,拓展了极化评估维度。分子影像方面,靶向 CD206 的 PET/CT 探针和基于 TTR1 的 MR 探针已实现肝转移灶 M2 浸润的活体可视化与定量^[44]。组织病理上,M1/M2 空间互作图谱联合免疫评分预后分层优于 TNM 分期,单细胞组学定义的 SPP1⁺、C1QC⁺ 亚群预测更精准^[45]。耐药层面,M2 型巨噬细胞的极化优势可驱动靶向治疗与化疗耐药^[46],M1/M2 型极化状态有望作为伴随诊断指标指导个体化治疗。治疗上,干预策略已形成清除 M2、重编程 M2 为 M1、增强 M1 功能三大路径。CSF-1R 抑制剂培西达替尼可缩减肝转移负荷,但单药疗效有限;CD40 激动剂恢复 M1 功能,联合 PD-1 抑制剂可逆转免疫耐药;STAT3 抑制剂与 PI3K γ 抑制剂分别阻断 M2 信号和诱导 M2 向 M1 转化;天然产物如黄芩素、小檗碱均可调控 M1/M2 平衡并减少肝转移结节^[47]。M2 重编程与免疫检查点抑制剂联用可提升 CD8⁺ T 细胞浸润,将“冷”瘤转化为“热”瘤,相关临床试验正在推进。

4 当前研究存在的问题与局限性

当前研究面临多重交织的瓶颈。在表型界定上,M1/M2 二分法标准混乱——CD163、CD206 在人肝 KCs 中组成性表达且可共标,中外研究检测判读尺度不一,使“M1/M2 比值”难以横向比对;单细胞组学揭示的 SPP1⁺促血管亚群、C1QC⁺免疫调控亚群远超二元框架,亟需多组学共识性分型^[48]。在机制层面,体外 LPS/IFN- γ 与 IL-4/IL-13 诱导难以模拟体内血流剪切、肝窦接触、代谢物梯度与缺氧波动等序贯信号的持续塑形;M1-M2 中间状态的功能特性与可逆条件不明,深部活体成像技术仍未突破^[49]。在转化方面,靶向精度与疗效均受制约;CSF-1R 等靶点并非巨噬细胞独有,阻断可耗竭 KCs 并致脱靶毒性;肝脏免疫耐受削弱重编程效果;KRAS、BRAF 等突变驱动 M2 亚群多样性,使单通路抑制后代偿旁路激活,乳酸、腺苷等代谢物亦可独立维持免疫抑制;且与化疗或免疫检查点抑制剂联用时,给药时序与剂量配比缺乏循证依据^[50]。

5 小结与展望

巨噬细胞 M1/M2 型极化失衡是结直肠癌肝转移核心免疫驱动力:M1 经抗原提呈、NO/ROS 杀伤、激活适应性免疫和抗血管生成阻断转移,M2 则借预转移微环境改造、EMT、促血管淋巴管生成和深度免疫抑制推动演进,二者平衡直接决定微小病灶被清除或进展。非编码 RNA(miR-155/21、lncRNA MM2P)、m6A 修饰、代谢重编程(琥珀酸-HIF-1 α 轴、IDO1-犬尿氨酸-AhR)及肠-肝轴等新层面极大拓展了极化上游调控网络;外泌体 CD163/CD206 液体活检、CD206 靶向分子影像及 CSF-1R 抑制剂、CD40 激动剂、STAT3/PI3K γ 抑制剂等策略正加速临床转化。但表型界定、动态解析、转化效能与互作网络等瓶颈仍然存在。未来需建立超越 M1/M2 的 TAM 功能分型共识,发展活体谱系追踪以揭示体内极化切换全貌,系统解析巨噬细胞与星

状细胞、肝窦内皮、Treg、MDSC 及菌群代谢物的多维互作,挖掘极化开关的决定性表观与代谢检查点,鉴定高特异、低毒靶点。临床上,外泌体极化标志物联合 ctDNA 的多参数液体活检模型有望实现高危者极早期预警和术后微小残留监测;M2 靶向分子影像可无创实时评估疗效;CSF-1R 抑制剂、CD40 激动剂等重编程策略联合免疫检查点抑制剂,有望将“免疫冷”肝转移灶重塑为“免疫热”表型,突破免疫治疗瓶颈。从极化平衡纠正到微环境全局重塑,巨噬细胞极化研究正成为肝转移免疫治疗范式变革的关键支点。

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