综　述　　结直肠癌手术及围手术期研究进展专题

结直肠癌肿瘤微环境的动态演变及其临床意义

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[摘要]　结直肠癌肿瘤微环境(TME)是由免疫细胞、基质细胞、细胞外基质及肠道微生物群构成的动态生态系统，在肿瘤发生、演进与耐药中发挥核心作用。本文系统阐明TME经历从炎症到癌转化、免疫逃逸到转移前微环境的重塑过程，揭示代谢重编程、缺氧与酸性景观及细胞通讯等肿瘤进化的关键驱动机制。微环境的高度异质性是导致“热肿瘤”与“冷肿瘤”对临床免疫治疗响应差异的核心因素。基于此，本文重点梳理重塑微环境的前沿干预策略，涵盖免疫检查点阻断、逆转“冷肿瘤”的多模态联合疗法、靶向基质与代谢网络以及重构“肠道菌群-免疫轴”的微生态调控，深度解析TME演变特征，为破解结直肠癌治疗瓶颈及推动个体化精准诊疗提供了关键理论支撑与转化思路。

[关键词]　结直肠癌；肿瘤微环境；微环境重塑；肠道微生态

The dynamic evolution and clinical significance of the tumor microenvironment in colorectal cancer

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[**Abstract**]　The tumor microenvironment (TME) in colorectal cancer is a dynamic ecosystem composed of immune cells, stromal cells, the extracellular matrix, and the gut microbiota, playing a central role in tumorigenesis, progression, and drug resistance. This review systematically elucidates the remodeling process of the TME, spanning the inflammation-to-carcinoma transition, immune evasion, and the establishment of the pre-metastatic niche. It highlights key driving mechanisms of tumor evolution, including metabolic reprogramming, hypoxic and acidic landscapes, and complex cellular communication. The high heterogeneity of the TME is a core factor underlying the differential responses of "hot" and "cold" tumors to clinical immunotherapy. Based on these insights, this article highlights cutting-edge intervention strategies aimed at remodeling the TME, encompassing immune checkpoint blockade, multimodal combination therapies designed to reverse "cold" tumors, strategies targeting the stroma and metabolic networks, and microecological modulation to reconstruct the "gut microbiota-immunity axis." An in-depth analysis of the evolutionary characteristics of the TME provides crucial theoretical support and translational insights for overcoming therapeutic bottlenecks and advancing personalized precision medicine in colorectal cancer.

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[**Key words**] colorectal cancer; tumor microenvironment; microenvironment remodeling; gut microbiota

根据最新流行病学数据显示，结直肠癌的发病率与死亡率分别高居全球恶性肿瘤第3位及第2位，约占癌症相关总死亡人数的10%[1]。面对日益严峻的生存挑战，传统的“肿瘤细胞中心论”在解析恶性演进及药物耐药机制方面已显现出瓶颈，这也驱动着研究视角向更宏观的系统生物学目标——肿瘤微环境(tumor microenvironment，TME)转型。TME是指恶性肿瘤赖以生存且持续交互的复杂局部内环境，是一个由多种组分构成的动态生态系统。在结直肠癌中，该系统不仅包含异质性的免疫细胞群、高度激活的肿瘤相关成纤维细胞(cancer-associated fibroblasts，CAFs)等基质成分，还涉及与物理强度增加相关的细胞外基质(extracellular matrix，ECM)以及由缺氧、酸化诱导的特异性理化景观[2-5]。此外，由于肠道独特的解剖特征，肠道微生物群作为核心生物组分，亦深度参与了TME的动态重塑，成为该微生态中不可或缺的一环[6-7]。

在从“正常黏膜-腺瘤-浸润性癌”的病理演变轴线上，TME并非一成不变，而是经历了从“免疫监视”到“免疫编辑”再到“免疫逃逸”的系统性重构[8-10]。这种动态进化网络不仅为肿瘤的克隆进化提供了免疫层面的许可，更在其代谢重编程、血管生成、远处转移及多药耐药过程中发挥关键调控作用[11-12]。基于上述背景，本文系统性综述结直肠癌TME的细胞与非细胞组成成分，深入探讨其在结直肠癌不同病理阶段的动态演变特征与分子机制，并重点梳理基于重塑TME的新型靶向、免疫以及基于肠道微生态的生物治疗策略，以期为结直肠癌的个体化精准治疗提供新的理论支撑。

1 结直肠癌TME的主要组成成分及其作用

1.1 免疫细胞 免疫细胞作为TME中异质性与功能可塑性最为突出的细胞类群，在结直肠癌中发挥双向调控作用。依据其在抗肿瘤免疫应答中的生物学功能，可划分为两大主要类别：(1)抗肿瘤免疫细胞。细胞毒性T细胞(cytotoxic T lymphocytes，CTLs)是执行抗肿瘤杀伤效应的核心细胞亚群，其在肿瘤组织中的高密度浸润通常预示着更好的预后[13]。在包括结直肠癌在内的多种实体瘤中，自然杀伤(natural killer，NK)细胞可通过非主要组织相容性复合体(major histocompatibility complex，MHC)依赖的方式识别并清除试图逃避免疫监视的癌细胞[14]。在先天免疫方面，经典激活的M1型巨噬细胞能够分泌肿瘤坏死因子(tumor necrosis factor，TNF)-α、白细胞介素(interleukin，IL)-12等促炎因子，吞噬并杀伤肿瘤细胞[15]。树突状细胞作为承担抗原递呈功能的细胞，负责摄取肿瘤新抗原并激活初始T细胞[16]。(2)促肿瘤免疫细胞。随着肿瘤的进展，微环境会逐渐“驯化”免疫细胞，使其转化为促癌表型。调节性T细胞(regulatory T cells，Tregs)通过分泌IL-10和转化生长因子(transforming growth factor，TGF)-β强效抑制CTLs的功能[17-18]。肿瘤相关巨噬细胞(tumor-associated macrophages，TAMs)极化为替代激活的M2型，其不仅丧失抗肿瘤能力，还可通过分泌血管内皮生长因子(vascular endothelial growth factor，VEGF)促进血管生成，并重塑ECM[19-20]。此外，骨髓来源抑制性细胞(myeloid-derived suppressor cells，MDSCs)的大量扩增和浸润，也是导致局部免疫耐受的核心因素[21-22]。

临床病理学上，根据结直肠癌TME中免疫细胞特征空间分布差异，还可将免疫细胞分为“免疫炎性型”(热肿瘤)与“免疫沙漠型”(冷肿瘤)[13，23-24]。“免疫炎性型”的特征是肿瘤实质内有大量活化的CTLs浸润，且伴有促炎性细胞因子的表达，这类微环境通常预后较好，对免疫检查点抑制剂(immune checkpoint inhibitors，ICIs)敏感[25]。相反，“免疫沙漠型”则缺乏免疫细胞的浸润，或者免疫细胞被致密的基质屏障阻挡在肿瘤外围(图1)，这类微环境代表了极端的免疫耐受状态，导致大多数结直肠癌患者对当前的免疫治疗药物无响应[23,26-27]。

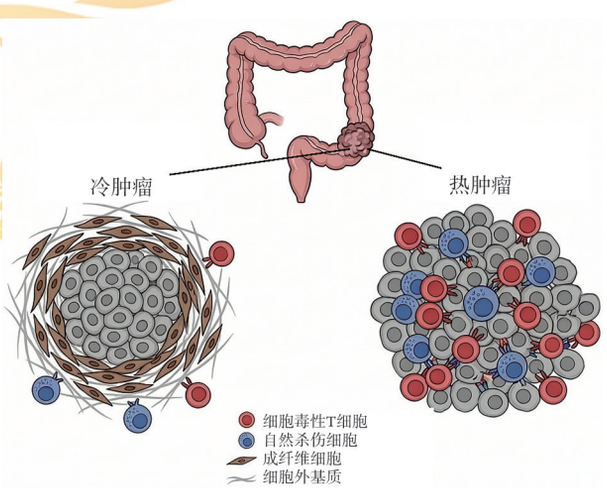

图1 不同类型的结直肠癌肿瘤免疫细胞浸润

Fig. 1 Tumor immune cell infiltration in different types of colorectal cancer

该图主要展示结直肠癌中两类典型肿瘤微环境的免疫细胞空间浸润特征。左侧代表“冷肿瘤”，其特征是致密的成纤维细胞与细胞外基质在肿瘤外围形成坚固的物理屏障，严重阻碍了效应免疫细胞的入渗；右侧代表“热肿瘤”，其特征是肿瘤实质内部有大量活跃的细胞毒性T细胞和自然杀伤细胞浸润，这类微环境通常对免疫治疗表现出较好的临床响应

1.2 基质细胞　CAFs是结直肠癌微环境中最丰富的基质细胞群体。不同于正常的成纤维细胞，CAFs处于持续激活状态。它们一方面通过分泌大量的生长因子直接促进结直肠癌细胞的增殖和干性[3,28-29]；另一方面，还可通过分泌基质金属蛋白酶(matrix metalloproteinases，MMPs)重塑ECM[30-31]。值得关注的是，密集的CAFs网络在肿瘤周围形成一道物理屏障，可阻碍化疗药物的递送和免疫细胞的浸润，这被认为是诱导结直肠癌产生治疗耐药的关键机制之一[32-33]。

血管与淋巴管内皮细胞也是结直肠癌TME中不可忽略的重要细胞组分，肿瘤的快速增殖需要大量的氧气和营养，这依赖于新血管的生成[34]。肿瘤细胞和TAMs分泌的VEGF促使内皮细胞异常增殖，形成结构扭曲、通透性极高且缺乏周细胞覆盖的肿瘤血管，这种异常血管网结构紊乱且有效灌注不足可导致局部微环境的严重缺氧，TME缺氧反过来又可刺激肿瘤分泌更多的VEGF，导致更多劣质血管生成，同时促使肿瘤细胞为了寻找氧气而发生转移[35-37]。此外，通透性极高的血管也为肿瘤细胞进入血液循环和淋巴系统提供了便利通道，促进结直肠癌细胞转移[38]。

1.3 ECM　在结直肠癌进展中，CAFs大量分泌胶原蛋白、纤连蛋白和透明质酸，导致ECM异常过度沉积。胶原交联酶的异常活跃可增加胶原纤维的交联度，显著增加基质硬度，从而构建出一种致密、僵硬的纤维化微环境[39-41]。这种力学信号的改变能够通过整合素受体传递入肿瘤细胞内部，激活Yes相关蛋白/含PDZ结合基序的转录共激活因子(YAP/TAZ)等机械转导通路，进而上调促进上皮-间质转化(epithelial-mesenchymal transition，EMT)的转录因子，这导致肿瘤细胞下调上皮标志物，丧失细胞间连接和极性；同时上调间质标志物，获得成纤维细胞样的运动能力和侵袭性。最终，这种表型转换赋予结直肠癌细胞突破基底膜、抵抗失巢凋亡并向远处器官转移的恶性潜能[2,42]。

1.4 肠道微生物群　与其他实体瘤不同，结直肠癌的发生处于肠道这一充满微生物的特殊环境中[43]。随着研究的深入，肠道微生物已被证实并非单纯的生物组分，而是结直肠癌TME的核心驱动因素之一[44-45]。为了系统理解肠道菌群如何参与肿瘤演进，笔者构建了一个菌群-免疫-代谢-基质的多维整合性调控框架。在该框架下，肠道致病菌与宿主细胞不再是单向的因果关系，而是通过错综复杂的网络互作，系统性地重塑结直肠癌的TME。

1.4.1 菌群-基质/上皮网络：破坏物理屏障与基因组稳定性　肠道微生物首先通过与肠道上皮及基质的直接作用作为肿瘤的发生创造条件。一方面，特定致病菌能分泌基因毒素直接破坏宿主细胞的基因组稳定性。例如，在肠道中存在一种携带聚酮合酶(polyketide synthase，PKS)基因岛的大肠杆菌(*PKS*$^+$ *E. coli*)，*PKS*$^+$ *E. coli*常与产肠毒素脆弱拟杆菌在肠道微环境中协同定植[46]。*PKS*$^+$ *E. coli*利用该基因簇合成具有基因毒性的大肠杆菌素，该毒素可通过烷基化诱导宿主细胞DNA发生严重的双链断裂；摩根摩根菌(*M. morganii*)也能分泌含亚胺基团的代谢物(吲哚亚胺)诱导DNA损伤，进一步引发基因组不稳定性及致癌突变的积累，从而直接驱动结直肠癌的发生[47-49]。另一方面，致病菌通过表面蛋白直接劫持上皮和基质细胞的致癌信号网络。例如，具核梭杆菌(*F. nucleatum*，*Fn*)通过其表面的梭杆菌黏附素A(FadA)与肠上皮细胞的E-钙黏蛋白(E-cadherin)结合，异常激活Wnt/β-catenin促癌通路；而厌氧消化链球菌(*P. anaerobius*)则通过识别基质细胞上的整合素α2β1，激活磷脂酰肌醇3-激酶-蛋白激酶B(PI3K-Akt)通路促进细胞增殖[50]。这些细菌与肠道细胞之间的互相作用共同导致肠道黏膜基质屏障的破坏，并在分子层面为细胞的早期恶性转化提供驱动力。

1.4.2 菌群-免疫网络：重塑炎症与免疫抑制性微环境　基质屏障的受损可进一步介导微生物与黏膜免疫系统的深度交汇，形成“慢性炎症-免疫逃逸”的恶性循环。*Fn*作为结直肠癌微环境中最受关注的致病菌之一，不仅能通过其表面黏附素FadA结合肠上皮细胞的E-cadherin，激活肠上皮细胞的Wnt/β-连环蛋白(Wnt/β-catenin)促癌信号通路，还能通过其表面的成纤维细胞激活蛋白2(FAP2)结合免疫细胞上的抑制性受体TIGIT(具有Ig和ITIM结构域的T细胞免疫受体)和癌胚抗原相关细胞黏附分子1(CEACAM1)，诱导T细胞和NK细胞凋亡，从而介导异常的肠上皮细胞的免疫逃逸[51-52]。最新研究还发现，*Fn*分泌的代谢物ADP-庚糖(ADP-heptose)可激活细胞内的α-激酶1(ALPK1)受体，诱发促炎反应，甚至上调程序性死亡配体1(programmed death ligand 1，PD-L1)的表达，从而抑制抗肿瘤免疫细胞的杀伤活性[53]。此外，肠道中的脆弱拟杆菌还能分泌BFT毒素(*Bacteroides fragilis* toxin，BFT)，该毒素可诱导辅助性T细胞17(T helper 17，Th17)极化并释放IL-17，从而营造出持续的局部炎症微环境。这不仅可破坏肠黏膜屏障，更加速肠上皮细胞从炎性增生向恶性肿瘤的演进[54-55](图2)。

1.4.3 菌群-代谢网络：宿主-微生物共代谢的系统性调控　肠道微生物介导的代谢重编程，作为连接环境因素(如饮食)与宿主TME的桥梁，呈现出全身性、多系统变化的调控特征[56-57]。一方面，高脂饮食等

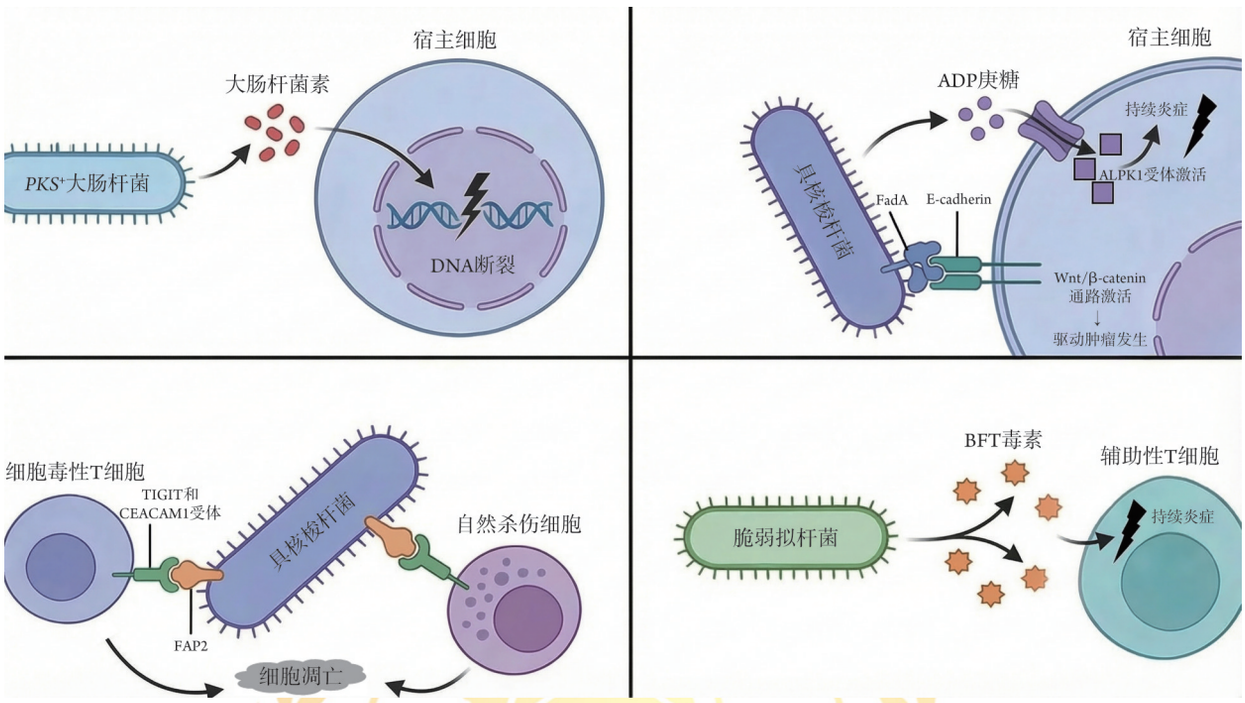

图2 肠道微生物的促肿瘤作用

Fig.2 The pro-tumorigenic effects of gut microbiota

该图系统总结了肠道微生态中关键致病微生物驱动结直肠癌发生与演变的分子机制：(1)携带*PKS*基因岛的大肠杆菌分泌基因毒素(如大肠杆菌素)，直接引起宿主细胞DNA双链断裂；(2)具核梭杆菌(*Fn*)通过表面FadA蛋白结合肠上皮细胞E-cadherin，异常激活Wnt/β-catenin促癌增殖通路，并通过分泌ADP-庚糖激活ALPK1受体诱发炎症；(3)*Fn*通过FAP2蛋白结合免疫细胞表面的抑制性受体(TIGIT和CEACAM1)，诱导具有杀伤功能的T细胞凋亡，介导免疫逃逸；(4)脆弱拟杆菌通过分泌BFT毒素诱导Th17细胞极化，破坏肠黏膜屏障并形成持续的局部慢性炎症微环境。PKS. 聚酮合酶；DNA. 脱氧核糖核酸；E-cadherin. E-钙黏蛋白；Wnt/β-catenin. Wnt/β-连环蛋白；ADP. 腺苷二磷酸；ALPK1. α-激酶1；FAP2. 成纤维细胞激活蛋白2；FadA. 梭杆菌黏附素A；TIGIT. 具有Ig和ITIM结构域的T细胞免疫受体；CEACAM1. 癌胚抗原相关细胞黏附分子1；BFT毒素. 脆弱拟杆菌毒素；Th17细胞. 辅助性T细胞17

环境因素可富集胆汁酸代谢菌(如特定梭菌属)，该细菌可将初级胆汁酸转化为脱氧胆酸等次级胆汁酸，引发强烈的氧化应激并激活核因子κB(nuclear factor κB，NF-κB)炎症通路，加速基质细胞衰老与突变，发挥显著的促癌效应[45,58]。另一方面，肠道内的有益共生菌(如丁酸梭菌和双歧杆菌等)可发酵水溶性膳食纤维产生的短链脂肪酸，在临床前模型中表现出显著的保护作用，其中丁酸作为天然的组蛋白去乙酰化酶(histone deacetylase，HDAC)抑制剂，可通过表观遗传途径恢复抑癌基因表达以诱导癌细胞凋亡，同时修复紧密连接蛋白以维持肠道黏膜屏障稳态[59-60]。

综上，肠道微生物驱动结直肠癌发生的机制，绝非若干孤立通路的简单叠加，而是一场由“菌群-免疫-代谢-基质”多维互作网络主导的系统性微环境重塑(图3)。在该互作网络下，基因毒素对上皮基质屏障的物理破坏、宿主-微生物共代谢的失衡以及免疫抑制细胞的异常趋化交织在一起，形成了互相放大的级联效应。最终，这种多维度的深度串扰共同构筑了一个高度免疫抑制、由慢性炎症驱动且代谢失调的促癌微生态系统[44,61]。

2 TME在结直肠癌发生发展中的动态演变过程

2.1 起始阶段：从炎症到肿瘤转变 结直肠癌的发展是一个多步骤的过程。在散发性或炎症性肠病相关的结直肠癌中，慢性炎症是TME重塑的初步特征[62-63]。在正常黏膜向炎性息肉和腺瘤演变的过程中，肠道屏障功能受损导致微生物产物渗入黏膜层，进而激活巨噬细胞释放大量炎性细胞因子。这些因子的聚集引发了信号通路的异常激活：如IL-6可通过结合其受体激活信号转导及转录激活蛋白3(signal transducer and activator of transcription 3，STAT3)信号通路，而TNF-α则激活NF-κB通路[64-65]。这两个关键转录因子不仅能上调抗凋亡基因，赋予发生突变的上皮细胞生存优势，还可进一步诱导环氧合酶2(cyclooxygenase-2，COX-2)和前列腺素E2(prostaglandin E2，PGE2)的产生[66-67]。持续的炎症可促使免疫微环境从“清除病原体”模式向“组织修复和免疫耐受”模式偏移，这是免疫监视功能受损的重要环节，可为携带早期突变(如*APC*基因突变)

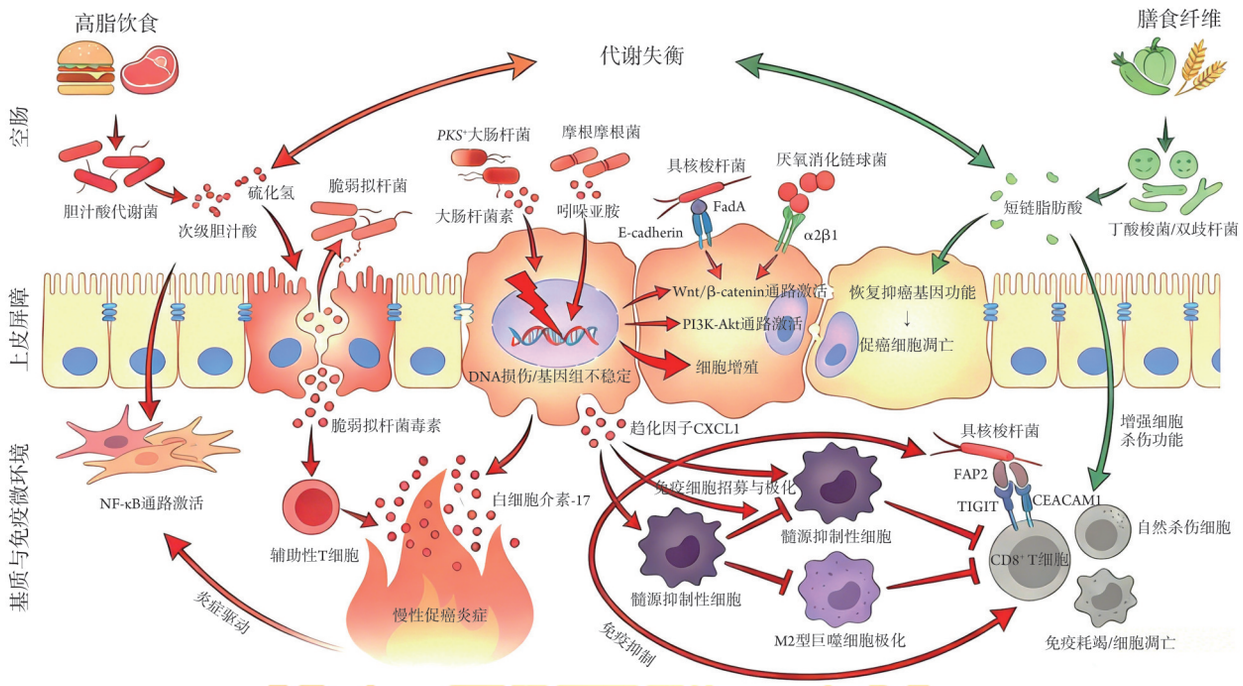

图3 菌群-免疫-代谢-基质互作网络

Fig.3 Microbiota-immunity-metabolism-matrix interaction network

该图刻画了结直肠癌中由“菌群-免疫-代谢-基质”多维互作构成的复杂促癌微生态网络。高脂饮食等环境因素导致胆汁酸代谢失衡，协同致病菌破坏肠道物理屏障并激活 NF-κB 炎症通路。致病菌(如具核梭杆菌、厌氧消化链球菌)通过特异性受体异常激活 PI3K-Akt 等通路促进肿瘤增殖；同时，微环境中大量招募免疫抑制性细胞(如 MDSCs、Tregs 及 M2 型巨噬细胞)，并释放细胞因子导致效应 $CD8^+$ T 细胞耗竭与凋亡，最终形成高度免疫耐受的级联放大网络。相对地，膳食纤维与有益双歧杆菌等通过产生短链脂肪酸，在维持屏障稳态中发挥保护作用。NF-κB. 核因子 κB；PI3K-Akt. 磷脂酰肌醇-3-激酶-蛋白激酶 B 信号通路；CXCL1. C-X-C 基序趋化因子配体 1；IL-17. 白细胞介素-17；M1/M2. M1 型(经典激活)/M2 型(替代激活)巨噬细胞；$CD8^+$ T 细胞. 细胞毒性 T 淋巴细胞；Tregs. 调节性 T 细胞；MDSCs. 骨髓来源抑制性细胞

的细胞提供存活的时间窗口[11,54,68]。

2.2 进展阶段：免疫逃逸与侵袭 当腺瘤恶变为腺癌后，TME 与肿瘤细胞的互相作用进入了“免疫编辑”的逃逸阶段和侵袭阶段[69]。为了躲避抗肿瘤免疫细胞的杀伤作用，结直肠癌肿瘤细胞会通过表观遗传或基因突变下调 MHC-I 分子的表达，使得 T 细胞无法识别肿瘤抗原[70]。同时，肿瘤细胞和浸润的髓系细胞会上调 PD-L1 的表达，并在 TME 中形成具有高度免疫抑制性的生化屏障，耗竭局部浸润的 $CD8^+$ T 细胞，最终导致肿瘤细胞的免疫逃逸[71]。

EMT 是肿瘤细胞发生侵袭转移的重要节点，其是指上皮细胞失去细胞间连接与极性，逐渐转变为间质样细胞的过程，细胞从“贴附”变为“迁移、侵袭”[72-73]。在 TME 中，CAFs 和炎性细胞分泌的 TGF-β、IL-8 等因子是诱导结直肠癌细胞发生 EMT 的核心驱动力。EMT 赋予了肿瘤细胞显著的间充质特征：细胞间的 E-cadherin 丢失，波形蛋白表达上调，细胞极性丧失，运动和侵袭能力显著增强[74]。这使得癌细胞能够降解基底膜，发生血管内渗，迈出转移的第一步[33]。

2.3 转移阶段：转移前微环境 肝脏是结直肠癌血行转移的首选靶器官[75]。研究表明，结直肠癌原发灶细胞可分泌富含特定整合素(如 αvβ5)、miRNA 及促炎因子的外泌体，经血液循环流向肝脏，被肝脏驻留的库普弗细胞及肝星状细胞(hepatic stellate cells，HSCs)特异性摄取，这一过程在结直肠癌肝转移的临床前模型中已得到验证[76]。这些外泌体作为关键信使，一方面激活 HSCs 促进纤连蛋白的分泌，重塑肝脏 ECM；另一方面，诱导趋化因子的释放，定向招募 MDSCs 聚集。这种经由外泌体远程“驯化”的肝脏微环境，呈现出高度的免疫抑制与血管通透性增强特征，为循环肿瘤细胞的归巢、存活及克隆性增殖奠定了基础[77-79]。

3 TME 影响结直肠癌进展的关键机制

3.1 代谢重编程 TME 中的代谢重编程(metabolic reprogramming)是近年来结直肠癌研究的重大突破。由于肿瘤细胞遵循瓦尔堡效应(Warburg effect)，即使在有氧条件下，它们也倾向于通过糖酵解途径快速获取能量[80]。肿瘤细胞大量消耗微环境中的葡萄糖、

谷氨酰胺等关键营养物质。这种剥夺效应可能限制周围CD8$^+$ T细胞的营养获取，抑制其克隆扩增并加速其向功能耗竭表型演变[22]。TME中的髓系细胞如TAMs和MDSCs高表达精氨酸酶1(arginase 1，ARG1)和吲哚胺2,3-双加氧酶(indoleamine 2,3-dioxygenase，IDO)，大量消耗微环境中的精氨酸和色氨酸，这些氨基酸是T细胞增殖所必需的[21]。色氨酸的代谢产物犬尿氨酸进一步诱导Tregs的生成，加剧免疫抑制[81]。

3.2 缺氧环境与酸性环境 由于结直肠癌新生血管结构紊乱且灌注效率低下，实体瘤内部普遍存在严重的物理性缺氧，这种应激状态诱导缺氧诱导因子1α(hypoxia-inducible factor 1α，HIF-1α)持续积累并进入细胞核，启动包括VEGF在内的多重促血管生成基因转录，形成恶性正反馈循环[82-83]。同时，缺氧驱动肿瘤细胞发生代谢重编程，肿瘤细胞高频糖酵解产生的大量乳酸被排入细胞外，导致TME呈现显著的酸性环境(pH 6.5~6.9)。酸性环境会直接抑制CD8$^+$ T细胞和NK细胞中穿孔素和颗粒酶的表达，削弱其细胞杀伤力[5]。在黑色素瘤等实体瘤模型中发现，Tregs和M2型巨噬细胞在酸性缺氧环境中不仅可存活，其免疫抑制功能还得到显著增强，这一现象在结直肠癌微环境中也得到了初步验证[84-85]。

3.3 复杂的细胞间通讯网络 在TME中，各类细胞通过极其复杂的通讯网络交织在一起。肿瘤细胞分泌的外泌体携带着大量的miRNA如促癌的miR-21和长链非编码RNA(long non-coding RNA，lncRNA)，它们可被传递给CAFs，促使CAFs向促肿瘤表型转化；也可进入免疫细胞内，干扰正常的抗原递呈和细胞因子的转录[86-87]。此外，趋化因子也是关键的通讯媒介：C-C基序趋化因子配体2(C-C motif chemokine ligand 2，CCL2)主导了外周血单核细胞向肿瘤局部的招募，并促使外周血单核细胞在微环境中分化为TAMs[88]。相反，C-X-C基序趋化因子配体9/10(C-X-C motif chemokine ligand 9/10，CXCL9/CXCL10)则是招募具有抗肿瘤活性的T细胞的关键因子[89]。微环境中这类促癌与抑癌通讯网络的失衡，最终决定了肿瘤的演变方向。

4 TME的异质性与分型

结直肠癌的TME并非千篇一律，其高度的异质性是导致患者预后不同和治疗响应差异的关键因素。

4.1 微卫星高度不稳定(microsatellite instability-high，MSI-H)/错配修复缺陷型(mismatch repair-deficient，dMMR)与微卫星稳定(microsatellite stable，MSS)/错配修复完整型(mismatch repair-proficient，pMMR)的微环境差异 在临床病理学中，基于DNA错配修复系统的功能状态，可将结直肠癌划分为具有截然不同分子特征与免疫景观的两大亚型：

(1)MSI-H/dMMR：该亚型约占结直肠癌总数的15%[90]。由于错配修复机制缺失，基因组在复制过程中积累了大量的移码突变，导致高肿瘤突变负荷(TMB)及大量免疫原性新抗原(neoantigens)的产生[91]。这种高免疫原性可诱导大量CD8$^+$ T细胞、Th1型辅助T细胞及成熟树突状细胞向肿瘤实质内浸润，从而构建高度活跃的“热肿瘤”微环境[92]。因此，MSI-H患者对ICIs表现出极佳的临床响应[93-94]。

(2)MSS/pMMR：该亚型约占据结直肠癌总数的85%[90]。因其基因组相对稳定且新抗原匮乏，TME多呈现“冷肿瘤”或“免疫排斥型”特征[92]。该类TME以致密的CAFs及胶原纤维组成的纤维化基质为核心，构成了阻碍免疫细胞入渗的物理屏障[93]。同时，Tregs及M2型巨噬细胞等免疫抑制细胞亚群的高度富集，可进一步下调肿瘤局部的免疫监视活性，显著拮抗机体的抗肿瘤应答。这种复杂的基质重塑与免疫耐受机制，使得MSS型患者对现有单药免疫治疗表现出显著的抗性，是目前临床亟待攻克的瓶颈[95-96]。

4.2 结直肠癌的TME分型演进 经典的结直肠癌共识分子亚型(CMS)实质上是基于转录组学对TME异质性的宏观刻画，各亚型在免疫浸润、基质活化及代谢重编程等维度展现出不同的微环境景观。具体而言，CMS1型(免疫型)多对应MSI-H状态，以极高的CD8$^+$ T细胞和Th1细胞浸润为特征，呈现出典型的“热肿瘤”表型，其基质活化程度相对较低，但常伴随程序性死亡受体1(PD-1)/PD-L1等免疫检查点的代偿性高表达。与CMS1型的高免疫浸润不同，CMS2型(经典型)与CMS3型(代谢型)均呈现显著的“免疫沙漠”特征。其中，由Wnt和MYC通路主导的CMS2基质活化程度极低，肿瘤细胞主要依靠活跃的生物合成与能量代谢快速消耗局部营养，形成不利于免疫细胞存活的代谢竞争微环境；而与*KRAS*突变高度相关的CMS3型则以显著的代谢重编程为核心，该亚型中的肿瘤细胞通过异常活跃的糖酵解、谷氨酰胺代谢和脂质生成在TME中积累大量乳酸，这种极端的酸性与代谢剥夺状态构筑了强效抑制抗肿瘤免疫的化学屏障。相比之下，CMS4型则呈现出相反的表型特征，以显著的基质活化为核心标志。该亚型富含持续激活的CAFs，伴随显著的EMT特征、大量胶原沉积和异常血管生成；这种致密的ECM不仅构成了坚固的物理屏障，还在TME中大量招募Tregs、M2型巨噬细胞等异质性免疫细胞亚群，最终塑造出高度免疫排斥的“冷肿瘤”景观，直接

导致其具有极强的侵袭性和最差的临床预后[10,97]。

随着单细胞转录组测序(scRNA-seq)技术的发展，TME的认知达到了前所未有的分辨率。多位学者在结直肠癌scRNA-seq领域做出了众多国际领先的突破[98-100]：其中一项研究阐述了dMMR/MSI-H型结直肠癌患者对PD-1阻断治疗产生应答的详细细胞类型与分子机制。研究表明，成功的ICI治疗不仅可激活多种抗肿瘤免疫细胞，重塑有利于淋巴细胞募集的基质环境，还可关键性地清除促肿瘤的炎症细胞。而在非应答者中，促炎微环境持续存在。这为理解ICI疗效机制、开发新的联合治疗策略以提高疗效提供了重要的生物学见解和潜在靶点[100]。在最新研究中，该团队还解析了新辅助治疗如何重塑直肠癌微环境，揭示了$CD8^+$ T细胞与I型非典型趋化因子受体$(ACKR1)^+$内皮细胞之间形成的促炎作用闭环是放大抗肿瘤免疫效应的核心机制[101]。基于此，在未来探索通过scRNA-seq在单细胞水平对微环境进行分型，可为探索结直肠癌新的免疫靶点和精准治疗提供分子级别的图谱[102]。

4.3 TME异质性驱动多药耐药的内在关联　TME的高度异质性是驱动结直肠癌多药耐药的核心因素。TME在空间分布与演化时序上的不均一性，通过免疫逃逸、代谢适应及基质屏障等机制的协同作用，显著降低肿瘤细胞对化疗及免疫治疗的敏感性[103-104]。首先，空间异质性导致“免疫炎性型”与“免疫排斥型”区域在同一瘤体内交织存在，这种分布的不均一性限制了效应T细胞的全面覆盖，使处于免疫抑制区的肿瘤细胞通过募集Tregs或下调抗原递呈水平实现获得性耐药[105-107]。其次，由于肿瘤血管分布不均引发的代谢异质性，导致TME内部存在显著的缺氧与酸化梯度，这不仅直接削弱细胞毒性药物的生物活性，还通过激活缺氧诱导因子介导的跨膜转运蛋白表达，增强肿瘤细胞的药物外排能力[108-110]。此外，基质组分的空间异质性分布形成了显著的物理防御屏障，局部高密度的ECM增加组织间隙流体压力(interstitial fluid pressure，IFP)，严重限制了大分子靶向药物及化疗药向肿瘤核心区域的渗透[111-112]。

鉴于TME异质性驱动耐药的复杂机理，未来的干预策略应由单一靶点打击转向多靶点联合重塑模式。通过血管正常化药物与基质降解手段的联合应用，有望打破物理与生化屏障，改善药物递送效率，同时结合代谢调节与免疫检查点阻断，实现对异质性TME的系统性重塑与耐药逆转。这种多维度的联合干预将是提升结直肠癌临床决策精准度与远期疗效的关键方向[113-116]。

5　基于TME的结直肠癌治疗策略

由于TME存在高度的时空异质性，结直肠癌的治疗策略正在从传统的“一刀切”模式，转向基于TME状态的精准分层干预。总体而言，对于占比约15%的MSI-H型结直肠癌，其TME具有高突变负荷和丰富的效应T细胞浸润，表现为“热肿瘤”特征，治疗核心在于通过单一ICI解除免疫耗竭状态，恢复既有抗肿瘤免疫[117-119]。而对于占比高达85%的MSS型结直肠癌，其TME常表现为紧密的基质包裹、异常血管增生及代谢拮抗的“免疫沙漠”或“免疫排斥”型“冷肿瘤”，单药ICI往往无效[120]。因此，当前的探索方向正逐步转向多维度的微环境重塑，即首先利用联合疗法(抗血管、化放疗)、靶向基质或微生态调控手段打破物理与化学屏障，将“冷肿瘤”转化为“热肿瘤”，再辅以免疫治疗以实现协同增效[121-122]。各策略在不同TME状态下的机制对比、证据分层及局限性详见表1[123-145]。

5.1 ICIs的应用　针对TME内免疫抑制状态进行干预的策略已取得重大突破，在结直肠癌中以靶向PD-1/PD-L1及细胞毒性T淋巴细胞相关抗原4(cytotoxic T-lymphocyte-associated antigen 4，CTLA-4)轴的ICIs最具代表性[146-147]。帕博利珠单抗及纳武利尤单抗等ICIs通过干预PD-1介导的免疫逃逸机制，能够有效恢复耗竭性T细胞的抗肿瘤活性，并在MSI-H/dMMR型结直肠癌中展现出卓越的临床疗效，重塑了该亚型患者的治疗模式[96]。临床研究证实，此类策略不仅可显著延长晚期患者的总生存期，更在新辅助治疗领域展现出较强的转化潜力[148]。在针对dMMR型结直肠癌的多项临床试验中，术前免疫干预使部分患者达到极高的病理完全缓解率[27,149-150]。这一成果不仅改变了结直肠癌的综合诊疗格局，也为从免疫微环境视角破解难治性肿瘤提供了关键的循证医学依据。

5.2 将“冷肿瘤”变“热”的联合治疗策略　MSS/pMMR型结直肠癌约占结直肠癌总数的85%，由于其固有的低免疫原性，单一免疫检查点阻断疗法往往难以奏效[147]。目前临床的重要发展方向在于通过多模态联合治疗策略重塑其“冷肿瘤”微环境[96]。

放疗与特定化疗药物联用可诱导肿瘤发生免疫原性细胞死亡。这一过程促使肿瘤细胞释放大量相关抗原及损伤相关分子，有效募集并激活树突状细胞，从而启动特异性$CD8^+$ T细胞免疫应答，实现微环境从“免疫沙漠型”向“炎性型”转化[13,23]。

对于常规治疗耐药的患者，抗血管生成药物与免疫治疗的联合方案正成为临床转化研究的关键方向。利用VEGF通路抑制剂(如小分子酪氨酸激酶抑

表1 基于不同结直肠癌肿瘤微环境特征的代表性干预策略及其临床循证依据评价

Tab. 1 Evaluation of representative intervention strategies and clinical evidence based on different tumor microenvironment characteristics in colorectal cancer

干预策略	代表性治疗方案	靶向微环境机制	适用人群	证据来源	证据等级	局限性与挑战
单药免疫检查点阻断	帕博利珠单抗、纳武利尤单抗	阻断免疫逃逸信号，重新激活已浸润但处于耗竭状态的效应T细胞	MSI-H/dMMR型、CMS1型	NCCN结肠癌临床实践指南(2026版)[123]；多项国际多中心随机对照试验(如KEYNOTE-177[124]、NICHE-2[125]等)	最高	对MSS型几乎无效；部分MSI-H患者存在原发性或获得性耐药
放化疗联合免疫治疗	放疗/特定化疗+PD-1抑制剂	诱导免疫原性细胞死亡，释放新抗原，招募树突状细胞和T细胞，实现“冷转热”	MSS/pMMR型	II/III期临床试验(如STELLAR系列研究[126])；肠癌放化疗联合免疫治疗相关中国专家共识[127]；Meta分析[128]	中/高	疗效异质性大；放化疗剂量与时机的选择(序贯 *vs.* 同步)尚无统一标准，过度放化疗可能反向耗竭免疫细胞
抗血管生成联合免疫	贝伐珠单抗、呋喹替尼+PD-1抑制剂	诱导异常血管正常化，缓解局部缺氧与酸性，逆转TAMs免疫抑制极化，促进T细胞入渗	MSS/pMMR型	II/III期临床试验(如FRESCO系列研究等[129-130])；真实世界研究队列[131-132]	高	血管正常化的时间窗口短暂且难以精准捕捉；抗血管药物剂量过高可能加剧缺氧，适得其反
靶向基质与成纤维细胞	FAP抑制剂、FAP-4-1BBL激动剂、TGF-β拮抗剂	消减CAFs，抑制胶原蛋白过度交联，降低组织间压，破坏物理屏障	CMS4型	临床前模型[133-134]；早期I/II期探索性临床试验[135-136]	低/中	CAFs存在显著的异质性，非选择性清除可能加速肿瘤进展；缺乏可靠的疗效预测生物标志物
靶向代谢重编程	IDO抑制剂、CD39/CD73抑制剂	纠正TME内的营养剥夺与酸性/代谢物堆积，恢复T细胞代谢稳态与杀伤力	CMS3型	细胞学基础研究及动物肿瘤模型研究[137-140]	低	肿瘤代谢途径具有高度代偿性和可塑性；干预肿瘤代谢容易损伤正常免疫细胞的代谢需求
肠道微生态调控	FMT、特异性噬菌体、工程化益生菌	清除致病菌，重塑宿主全身及局部免疫网络，促进新生抗原递呈	天然或获得性免疫治疗耐药人群、伴有严重肠道菌群失调的MSS型	肠菌移植应用于肿瘤治疗中国专家共识[141]；高水平基础研究[142-144]；小样本概念验证性临床试验[145]	中(概念验证)	FMT供体筛选标准尚未标准化，存在病原体传播风险；活菌制剂的定植效率、生物利用度及体内安全性仍需长期评估

文献检索策略：该表纳入的治疗策略及证据评价基于对PubMed、Web of Science、Cochrane Library及ClinicalTrials.gov数据库的系统性文献检索。主要检索词包括“colorectal cancer(结直肠癌)”“tumor microenvironment(肿瘤微环境)”“immunotherapy(免疫治疗)”“clinical trial(临床试验)”“meta-analysis(荟萃分析)”及各具体干预靶点名称等。检索时间范围为建库至2026年4月。纳入与排除标准：(1)最高/高等级证据：优先纳入现行权威指南(如NCCN指南)、发表于顶级医学期刊的III期随机对照试验(RCT)及高质量Meta分析；(2)中等证据：纳入具有明确临床获益趋势的II/III期临床试验或已发表的专家共识及概念验证(proof-of-concept)临床研究；(3)低/中等证据：主要纳入发表于高水平期刊的体内动物肿瘤模型及早期I/II期探索性试验。排除缺乏适当对照、样本量过小或研究设计存在重大缺陷的文献。证据等级判定标准：证据等级的划分以牛津循证医学中心(OCEBM) 2011版证据分级体系为核心框架，同时结合肿瘤临床研发阶段及临床获批/指南推荐状态进行综合评价，具体对应关系如下：最高(I级临床证据)：对应OCEBM 1级证据(含高质量随机对照试验(RCT)系统评价、单个窄置信区间RCT或“全或无”病例系列)，且已获药品监管机构批准或权威肿瘤指南(如NCCN、CSCO)推荐，代表循证医学中最高强度的临床证据。中/高(II–III期临床试验)：对应OCEBM 1b/2级证据，指完成III期RCT并展现明确临床生存获益，或处于II–III期临床探索阶段，已具备一定临床验证基础但尚未广泛获批一线应用。高(III期临床获批/推荐)：特指完成III期RCT且结果阳性，获得药品监管机构批准或权威指南推荐，等价于OCEBM 1b级证据，为肿瘤领域可直接实践的高级别证据。低/中(基础研究及早期临床试验)：对应OCEBM 4/5级证据，指处于I/II期临床探索阶段，或仅基于基础研究/动物模型，缺乏大规模临床验证，证据强度较弱。中(概念验证)：对应OCEBM 2b/3级证据，指在小样本探索性研究中观察到初步临床信号，具备潜在临床价值但尚未经大规模III期试验确证。MSI-H. 微卫星高度不稳定；dMMR. 错配修复缺陷型；MSS. 微卫星稳定；pMMR. 错配修复完整型；CMS. 共识分子亚型；NCCN. 美国国立综合癌症网络；PD-1. 程序性死亡受体1；TAMs. 肿瘤相关巨噬细胞；FAP. 成纤维细胞激活蛋白；FAP-4-1BBL. 靶向肿瘤的T细胞共刺激激动剂；TGF-β. 转化生长因子-β；CAFs. 肿瘤相关成纤维细胞；IDO. 吲哚胺2，3-双加氧酶；TME. 肿瘤微环境；FMT. 粪菌移植

制剂呋喹替尼、瑞戈非尼或大分子抗体贝伐珠单抗)不仅能通过阻断血供“饥饿”肿瘤，更能在特定剂量下诱导肿瘤异常血管发生“正常化”[96,129]。血管结构的优化可显著缓解局部微环境的缺氧与酸化状态，逆转TAMs的免疫抑制极化，并清除物理屏障以促进效应T细胞的有效入渗，这种微环境的系统性重塑，最终与PD-1/PD-L1抑制剂产生显著的协同增敏效应，为MSS型结直肠癌的临床治疗提供了新的范式[96,151-152]。

5.3 靶向基质与代谢的创新探索 针对以基质成分显著浸润为典型特征的CMS4型结直肠癌，对细胞外的基质物理屏障进行消减与干预是一个重要的方

向[153]。研究者正致力于开发靶向FAP蛋白的特异性抑制剂或TGF-β通路拮抗剂。此类策略旨在通过失活肿瘤相关CAFs，阻断其驱动的胶原纤维过度沉积与ECM重构，从而在物理层面软化肿瘤间质、降低组织间压，该策略在临床前模型中已被证实可显著提升化疗药物的转运效率与效应淋巴细胞的募集深度[154-155]。

TME中存在严峻的营养耗竭与免疫抑制性代谢产物堆积，因此以精准调节代谢竞争景观为目标的代谢调节剂的应用成为另一前沿方向[156]。通过抑制IDO途径、阻断腺苷信号轴(如CD39/CD73抑制剂)或干扰谷氨酰胺代谢，可有效纠正肿瘤细胞与免疫细胞间的代谢拮抗，恢复效应T细胞的代谢稳态与杀伤潜能[21,157]。尽管部分候选药物在临床转化过程中仍面临复杂挑战，但其作为重塑TME生化景观的重要策略，在临床前研究中已显现出巨大的转化潜力与应用前景[5]。

5.4 调节肠道菌群 鉴于肠道微生物群在结直肠癌演进及TME稳态维持中的核心地位，构建“肠道菌群-免疫轴”的干预策略已成为打破肿瘤免疫豁免、提升系统性治疗敏感性的前沿路径，通过靶向重塑肠道微生态来优化抗肿瘤免疫应答，正逐步从理论探讨走向临床转化[158-159]。

在精准微生态调控层面，采用定向清除与益生机制协同是重塑TME的关键。针对促癌致病菌的特异性清除是打破免疫抑制的基础。大量研究证实，*Fn*作为核心促癌菌，不仅可诱导免疫细胞的耗竭与肿瘤细胞的免疫逃逸，还可通过激活上皮细胞的自噬通路，介导对5-氟尿嘧啶(5-FU)及奥沙利铂的获得性化疗耐药[52,160]。由于传统广谱抗生素容易导致微生态进一步失调，利用特异性噬菌体靶向裂解*Fn*的疗法，已在结直肠癌临床前模型中展现出良好的应用潜力，通过靶向清除促癌致病菌策略，可逆转病原体介导的化疗耐药，同时解除局部免疫抑制、重新激活微环境中的抗肿瘤免疫级联反应[161]。

补充关键益生菌及其活性代谢产物是重塑微环境的另一方向。多项研究显示，嗜黏蛋白阿克曼菌和特定双歧杆菌，可通过空间占位竞争抑制致病菌定植；其中嗜黏蛋白阿克曼菌在结直肠癌动物模型中，可通过其细胞壁组分激活树突状细胞的Toll样受体2(TLR2)通路，增强树突状细胞的抗原递呈能力与I型干扰素分泌，显著提升肿瘤实质内$CD8^+$ T细胞的浸润丰度[162-164]。另一项研究表明，健康人来源的粪便微生物移植通过增加乳杆菌、阿克曼菌、伊莱氏菌和粪杆菌属等有益菌的丰度，并关联亚油酰乙醇胺等保护性代谢产物的变化，从而抑制小鼠结直肠癌的进展[165]。此外，在黑色素瘤模型中，由柔嫩梭菌(*Faecalibacterium prausnitzii*)等分泌的短链脂肪酸，作为HDAC抑制剂，能够通过表观遗传途径上调$CD8^+$ T细胞中IL-12受体的表达，增强效应T细胞的杀伤活性，并抑制MDSCs及Tregs的扩增，从代谢及表观遗传方面进行系统性免疫网络重塑[166]。

在临床上，粪菌移植(fecal microbiota transplantation，FMT)作为一种系统性免疫微环境的重塑策略，在逆转ICIs耐药方面，已在部分瘤种的临床研究与结直肠癌临床前模型中展现出潜在价值。FMT通过整体性重组受者的肠道微生物组，能够实现肠道生态网络的恢复与免疫微环境的系统性改善。例如，在2021年发表于*Science*的经典黑色素瘤临床研究中，研究者将对PD-1抗体响应良好患者的粪便菌群移植给既往治疗无效的耐药患者，成功重塑了受体的肠道及全身免疫图谱，诱导了肿瘤浸润淋巴细胞(TILs)的再激活，并有效逆转了耐药状态[167]。由于超过90%的结直肠癌属于MSS型，其微环境呈现缺乏免疫细胞浸润的“冷肿瘤”特征，对ICIs天然耐药[96]。已有临床研究表明，FMT通过移植健康供体或超级响应者的功能菌群，能够打破机体原有的免疫耐受屏障，其与ICIs联用不仅有望协同诱导肿瘤新抗原的释放，更能增强效应T细胞向瘤体内部的趋化浸润，从而驱动“冷肿瘤”向“热肿瘤”转变，从系统层面实现对MSS型结直肠癌微环境的根本性重塑[145,168]。

5.5 基于TME动态演变的时序性干预策略与耐药监测 TME的演进贯穿结直肠癌发展的全过程。在目前的临床探索中，传统的多药同步联合模式有时会面临药物靶点拮抗或毒副反应叠加的局限[120]。因此，基于TME动态特征构建时序性干预理论框架，正成为转化医学领域探索克服治疗瓶颈的前沿方向[169-170]。该策略构想依据肿瘤基质与局部免疫状态的演变规律，探索分阶段靶向治疗的潜在可行性：

(1)破除组织屏障与诱导微环境正常化：针对伴有严重纤维化基质和重度缺氧特征的MSS型结直肠癌，多项临床前研究提示，初始干预的重点或可聚焦于微环境的物理与生化屏障，而非直接激活免疫细胞[104,171]。例如，探索性研究表明，率先应用特定剂量的抗血管生成药物有望诱导肿瘤异常血管网趋于正常化[172-173]。此外，已有研究证实TGF-β抑制剂可减少ECM的过度沉积[174]。此阶段的前置性干预理论上可降低肿瘤组织间质压并改善微循环灌注，从而缓解缺氧与酸性代谢状态，为后续药物的递送与效应细胞的浸润创造有利的空间条件[175]。

(2)免疫激活与微生态协同重塑：在微环境血管与基质屏障得到初步改善的潜在时间窗口内，序贯引入ICIs被证实能够更有效地促进效应$CD8^+$ T细胞

向肿瘤实质的浸润并发挥杀伤作用[120]。此外，部分转化研究提出，在此节点协同探索肠道微生态调控(如FMT或特异性噬菌体干预)，可能依托“肠道-免疫轴”机制，进一步增强局部及系统性抗肿瘤免疫应答[176-177]。尽管相关概念在动物模型及早期试验中初见端倪，但其最佳给药顺序与时间间隔仍有待临床数据的确证。

(3)基于微环境演变的动态耐药监测与方案调整：TME在治疗压力下的代偿性重塑是引发获得性耐药的重要机制[171]。未来，结直肠癌的耐药管理有望依托多维度的实时监测体系展开。例如，探究运用液体活检技术动态追踪循环肿瘤DNA(ctDNA)的克隆演化特征，并结合粪便宏基因组学监测肠道微生物(如*Fn*)丰度的致病性波动[178-180]。当分子层面捕捉到TME向高度免疫耐受或代谢拮抗状态转变的早期信号时，可为临床提供干预窗口，指导在影像学进展发生前适时进行靶点的调整[178,181]。以上研究为实现结直肠癌的闭环管理提供了新思路，但将其完全转化为常规临床实践，仍需依赖大规模前瞻性临床试验进一步验证。

对结直肠癌TME异质性及其分子交互机制的深度解析，已成为驱动临床干预策略革新的核心引擎。目前，通过精准调控基质硬度、逆转免疫抑制景观及纠正代谢重编程等“微环境重塑”手段(图4)，正显著拓宽肿瘤治疗的维度，为改善患者远期预后及破解治疗抗性提供了全新的系统性参考[23,31,81,97]。

未来，依托多组学测序与合成生物学的跨学科融合，经基因工程重塑的“下一代益生菌(next-generation probiotics，NGPs)”将展现出巨大的临床潜力。作为新型活菌药物平台，它们不仅能实现药物的精准肿瘤靶向递送，更具备在肿瘤局部触发高效原位免疫调节的核心功能。综上，靶向“肠道菌群-免疫轴”不仅为结直肠癌的机制研究提供了全新视角，更将通过个性化、精准化的微生态干预手段，为攻克免疫治疗应答瓶颈、改善结直肠癌患者预后提供了潜在的临床转化方向[182]。

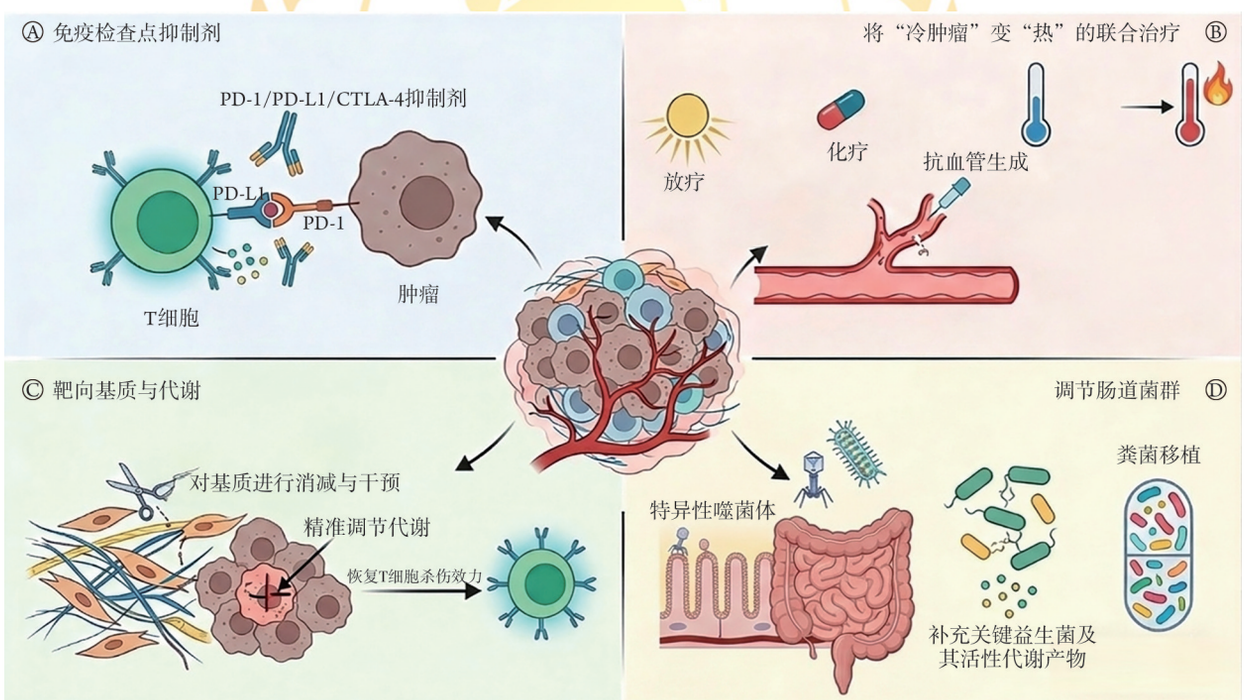

图4 基于肿瘤微环境(TME)的结直肠癌治疗策略

Fig.4 Colorectal cancer treatment strategies based on TME

该图展示了基于TME异质性特征的结直肠癌前沿多维干预策略。①针对已有免疫细胞浸润的“热肿瘤”，通过单药免疫检查点抑制剂(如抗PD-1/PD-L1、CTLA-4抗体)阻断免疫逃逸信号，恢复T细胞杀伤力；②针对免疫排斥型肿瘤，利用放化疗和抗血管生成药物打破微环境屏障，实现将“冷肿瘤”转化为“热肿瘤”的策略；新兴的微生态及代谢重塑干预，包括消减基质纤维化与精准调节代谢网络(③)，以及通过粪菌移植、特异性噬菌体和补充活性益生菌等手段重构“肠道菌群-免疫轴”(④)，以期克服现有治疗耐药并实现精准协同增效。PD-1. 程序性死亡受体1；PD-L1. 程序性死亡配体1；CTLA-4. 细胞毒性T淋巴细胞相关抗原4

6 总结与展望

结直肠癌已不再被单纯视为由基因突变驱动的腺上皮细胞恶性增殖疾病，而是一个由肿瘤细胞、免疫细胞、基质细胞、ECM及肠道微生物群共同交织而成的复杂微环境生态系统[81,147,158-159]。TME在结直肠癌的起始、演变、转移及耐药过程中发挥着至关重要的调控作用。从“免疫监视”的失效到“转

移前微环境”的建立，深刻揭示了结直肠癌发展背后的多维度调控网络[11,13,81]。

尽管人们对TME的认知取得了长足进步，但临床转化仍面临重要挑战。首先，结直肠癌TME存在极高的时空异质性，这使得单一的靶向治疗容易产生获得性耐药[148,160,183]。其次，目前的体内外研究模型如细胞系、患者来源类器官、转基因小鼠等由于缺乏完整的免疫系统或无法真实模拟人体复杂的肠道微生态，仍无法全面复刻人体TME的多维动态特征。

未来，前沿技术的发展与应用将不断突破现有研究瓶颈。scRNA-seq技术与空间转录组学的深度融合，不仅能够精准描绘TME内高度异质性的细胞亚群图谱，更实现了对细胞间物理邻域关系与三维空间构筑的深度还原，从而揭示了微环境内部复杂的交互网络[8,30,98]。多重免疫荧光和质谱流式技术的普及，将使得从一份微小的活检样本中解读出海量的微环境信息成为可能[184-188]。

基于TME演变及异质性特征的个体化精准治疗，已成为突破结直肠癌治疗瓶颈的核心驱动力及未来临床干预的重要方向。寻找特异性强的新型TME生物标志物将用于指导患者的早期筛查、预后评估及治疗分层。随着将“冷肿瘤”转化为“热肿瘤”的联合免疫策略逐步探索，结合微生态调节、代谢重编程干预与传统放化疗，全面干预并重塑TME，有望为晚期结直肠癌患者改善生存预后提供新的治疗路径。

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