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·综 述·

肠道菌群在肿瘤化放疗及免疫治疗中的作用及其机制

The role of gastrointestinal microbiome in chemotherapy, radiotherapy and immunotherapy for cancer and its mechanism

陈菲 综述,白日兰,崔久嵬 审阅(吉林大学 第一医院 肿瘤中心,吉林 长春 130021)

[摘 要] 近年来研究显示,肠道菌群不仅与肿瘤的发生、发展和转移有关,还可通过参与化疗药物代谢导致化疗相关性肠炎、激活或调控免疫反应及信号通路、促进细胞因子的产生、修复肠道黏膜损伤等多种途径影响肿瘤患者对化疗、放疗和生物治疗的疗效和不良反应。肠道菌群种类繁多、丰度可变,个体差异性是患者对抗肿瘤治疗产生不同反应的原因之一。而肠道菌群受不同外源性因素的影响,故对其干预或重塑将增强抗肿瘤治疗的疗效和减轻治疗相关的毒副作用,改善肿瘤患者的生活质量和预后。本文就肠道菌群对化疗、放疗和免疫治疗的调控作用及相关机制,就靶向肠道菌群的治疗以提高抗肿瘤疗效、降低或预防毒副反应作一综述。

[关键词] 肠道菌群;肿瘤;化疗;放疗;免疫治疗
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肠道菌群是寄居在人体肠道内的正常微生物群落,对宿主的生长发育、营养代谢及免疫稳态都有重要作用。肠道菌群间保持共生或拮抗关系,可在肠道内形成一个动态平衡的生态系统,维持肠道屏障稳态,调控代谢、炎症和免疫[1]。特定肠道菌群作为促癌或抑癌因素,影响肿瘤的发生、发展和转移[2-8]。同时其可从多个方面影响药物的药代动力学、抗癌活性和毒性[4, 9],对抗肿瘤治疗产生重要影响。肿瘤患者对治疗反应的异质性和对毒副作用的易感性,可能一定程度上源于个体间肠道菌群组成和活性的差异[10]。肠道菌群主要通过以下机制直接或间接地影响抗肿瘤治疗:(1)菌群移位激活抗肿瘤T细胞免疫应答;(2)通过TLR和髓样分化初级应答分子88(myeloid differentiation primary response 88, MyD88)通路调控免疫反应;(3)分泌特定酶介导外源性药物或内源性物质代谢;(4)肠道菌群丰度及多样性改变。肠道菌群的构成受饮食、生活方式[11]及抗生素使用的影响[12],因此通过改变饮食、应用抗生素、补充益生菌、粪便菌群移植等方法调节肠道菌群增强抗肿瘤治疗疗效,减轻甚至治愈抗癌药物的不良反应,靶向肠道菌群的抗肿瘤治疗策略有望为肿瘤患者带来新希望。

1 肠道菌群对化、放疗的影响

1.1 对化疗疗效的影响

1.1.1 细菌移位及丰度改变激活炎症细胞而增强化疗疗效 接受环磷酰胺(cyclophosphamide, CTX)治疗的荷瘤小鼠,其肠道中革兰阳性(gram positive, G^+)海氏肠球菌(enterococcus hirae)向肠系膜淋巴结移位增多,可通过与核苷酸结合寡聚化结构域蛋白2(nucleotide - binding oligomerization domain-containing protein 2, NOD2)结合,增加肿瘤内$CD8^+$T细胞/Treg细胞比例,并激活Th17和记忆性Th1细胞免疫应答[13-14];同时肠道中革兰阴性肠原巴氏杆菌丰度增加,也通过与NOD2结合而促进IFNγ诱导性γδT细胞在肿瘤病灶中的浸润并产生记忆性Th1细胞,海氏肠球菌和肠原巴氏杆菌记忆性Th1细胞与晚期肺癌或卵巢癌患者的预后相关[13]。铂类化合物可通过致DNA交联而诱导肿瘤细胞凋亡,铂类的抗肿瘤疗效需要肠道菌群的辅助,细菌与天然免疫受体结合后由MyD88作为关键分子介导信号传递,激活肿瘤相关炎症细胞产生活性氧(reactive oxygen species,

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[作者简介] 陈菲(1994-),女,硕士生,主要从事肿瘤综合治疗的基础和临床研究,E-mail: 1527288819@qq.com
[通信作者] 崔久嵬(CUI Jiuwei, corresponding author),博士,教授,主任医师,博士生导师,主要从事肿瘤发病机制及免疫治疗研究,E-mail:cuijw@jlu.edu.cn

ROS），ROS破坏肿瘤细胞DNA，从而增强铂类药物杀伤肿瘤细胞DNA的作用[15]。

1.1.2 通过TLR4-MyD88通路及药物代谢酶降低化疗疗效 具核梭杆菌不仅参与结直肠癌的发生、发展及转移，而且与化疗耐药密切相关。一项使用小鼠模型的研究[16]发现，具核梭杆菌可通过作用于结直肠癌细胞TLR4以及MyD88通路，下调miR-4802和miR-18a*的表达，继而激活肿瘤细胞自噬导致化疗耐药，而自噬抑制剂及这两种miRNA的类似物可抑制该种耐药。另有研究[17]证明，甲硝唑能够减少具核酸杆菌数量并使肿瘤缩小，提示具核酸杆菌阳性肠癌患者化疗前应用抗具核梭杆菌或者抗自噬治疗，可能会增强化疗效果。胰腺癌患者的胰腺组织中存在大量细菌，这些细菌诱导化疗耐药并协助癌细胞转移。γ-变形菌是胰腺导管腺癌组织中的优势菌，可通过表达胞苷脱氨酶将吉西他滨（2',2'-二氟脱氧胞苷）代谢为其无活性形式2',2'-二氟脱氧尿苷，从而导致吉西他滨耐药，而环丙沙星的杀菌作用可逆转这种耐药[18]。

1.1.3 对化疗药物毒性的影响 肠道菌群主要通过产生药物代谢酶影响化疗的代谢以及参与TLR信号通路导致黏膜炎和神经毒性。（1）药物代谢酶：伊立替康（irinotecan）的非活性形式SN-38-G在肠道中可被细菌β-葡萄醣醛酸酶转化为有活性的SN-38，作用于快速增殖的肠道上皮细胞，进而引起剂量限制性肠道毒性[19]。应用抗生素减少表达β-葡萄糖醛酸酶的细菌数量或应用特异性细菌β-葡萄糖醛酸酶抑制剂，可预防和治疗伊立替康引起的肠道毒性，甚至可能提高伊立替康的最大治疗剂量而提高肿瘤控制率[20-21]。此外，临床研究[22]证明，口服益生菌可降低伊立替康相关腹泻的发生率及严重性。故在临床应用中，化疗前预防性服用益生菌或β-葡萄糖醛酸酶抑制剂或抗生素或许对接受伊立替康化疗的患者有重要意义，但仍需更多研究证明。（2）TLR信号通路：化疗药物导致肠道菌群改变，细菌产物或内源性损伤相关分子模式（damage associated molecular pattern，DAMP）与TLR4异常结合，激活异常的细胞因子风暴加重肠道黏膜损伤，TLR4基因被敲除的小鼠中，伊立替康和甲氨蝶呤（methotrexate, MTX）的肠道毒性症状均有所改善[23-24]。与TLR4作用相反，TLR2被共生菌活化后，可通过增加ATP结合盒式转运蛋白（ATP-binding cassette transporters, ABC transporters）中多药耐药蛋白1（multi-drug resistance protein 1，MRP1）的表达，使肠上皮细胞外排药物增多，减轻MTX诱导的黏膜损伤[23, 25]。研究[26]证明，G⁻菌胞壁成分脂多糖（lipopolysaccharides, LPS）在奥沙利铂（oxaliplatin, OXA）所致的机械性痛觉过敏中发挥了关键作用。LPS激活造血细胞及巨噬细胞表面的TLR4，刺激细胞分泌IL-6和TNFα等炎症因子而诱发机械性痛觉过敏。

1.2 对放疗疗效的影响

局部照射可诱导肿瘤细胞免疫原性死亡（immunogenic cell death，ICD），促进全身炎症和免疫[27]。电离辐射在辐射区域外产生的抗肿瘤反应即远隔效应，需激活APC和T细胞[28]。但关于微生物能否调控以及如何调控放疗疗效的研究还相对较少。鉴于肠道菌群在化疗和免疫治疗中都能影响ICD所引起的免疫应答[14-15, 29]，肠道微生物群是否在放疗的免疫激活中发挥作用值得深入探究。

菌群失调促进黏膜炎的发生和发展。接受放疗的患者及小鼠，其消化道上皮表面菌群组成的变化可促进口腔黏膜炎、腹泻、肠炎[30-32]；接受放疗的鼻咽癌患者，口腔菌群的变化与放疗所致黏膜炎的进展相关[33-34]；针对微生物群的干预措施可用于早期预测和预防放疗期间严重黏膜炎的发生[33]。放疗可诱导肠隐窝细胞凋亡，破坏肠道屏障及菌群组成[35]，使得致病菌激活肠道免疫系统而引发肠道炎症[31, 36]。盆腔放疗导致肠道菌群失调，诱导肠黏膜分泌IL-1β，促进辐射诱导的结肠损伤。重塑肠道菌群或直接抑制IL-1可能成为降低辐射诱导肠道损伤的潜在治疗方法[37]。

2 益生菌和粪便菌群移植改善炎症反应

FOLFOX化疗方案（5-FU、亚叶酸钙和OXA）诱导核转录因子-κB（nuclear factor-kappa B，NF-κB）活化，导致促炎细胞因子TNF、IL-1β和IL-6的上调而导致黏膜损伤。益生菌鼠李糖乳杆菌Lcr35通过抑制NF-κB活性，可改善FOLFOX方案诱导的黏膜炎[38]。口服冻干乳酸杆菌和双歧杆菌的益生菌组合，可预防顺铂的肠道毒性[39]。粪便菌群移植（fecal microbiota transplantation, FMT）也有助于防治化疗相关急性肠道炎症和黏膜屏障功能障碍，且未发现不良反应[40]。乳酸杆菌可预防顺铂引起的心脏毒性[41]，也可能是由于抑制了心肌炎症反应。益生菌鼠李糖乳杆菌GG（LGG）可激活TLR2，通过将表达环氧合酶2的细胞从绒毛转移到肠隐窝底部[42]，诱导ROS激活核转录因子NF-E2相关因子2（NF-E2 related factor 2，Nrf-2）信号通路，从而保护肠黏膜免受化疗或放疗所致的毒性[43-44]。在一些临床研究中，已经证明益生菌有益于预防辐射诱发的肠病。含有乳酸杆菌、双歧杆菌、干酪乳杆菌的制剂（如VSL＃3制剂），可预防盆腔放疗引起的肠道毒性，显著降低严重腹泻的发

生率，延缓洛哌丁胺的使用[31, 45]。头颈癌患者接受放疗和化疗期间给予短乳杆菌CD2锭剂也可降低放疗所致黏膜炎的发病率并提高治疗完成率[46]。FMT能重塑辐射小鼠的肠道菌群组成，上调与免疫及代谢调节相关的mRNA和lncRNA的表达，提高小肠组织VEGF水平，增加杯状细胞的数量和肠道黏液层厚度，改善肠道功能和上皮完整性，最终减轻辐射诱导的肠道毒性，提高辐照小鼠的存活率[47]。上述研究提示，FMT可能被用作辐射诱导肠道损伤的新型治疗方法，改善放疗患者的预后。深入研究放疗与肠道菌群的关系及菌群干预的调节机制将对提高治疗效果、减少治疗并发毒副反应具有重要意义。

3　肠道菌群对免疫治疗的影响

肠道菌群调控机体的抗肿瘤免疫。近期有研究[48-49]发现，梭菌属细菌通过介导初级胆汁酸的代谢而减少肝肿瘤中NKT细胞的聚集，进而促进肝癌的发展。近年来免疫治疗成为肿瘤研究领域的热点，得到临床应用的疗法主要包括细胞过继性T细胞治疗（adoptive T cell therapy，ACT）及免疫检查点抑制剂（immune checkpoint inhibitor，ICI）。免疫治疗可改善多数肿瘤患者的预后，但其疗效及不良反应存在个体差异。肠道菌群对免疫治疗的影响使得免疫治疗的应用更加有效和安全。

3.1　对ACT疗效的影响

先前研究[50]发现，肠道细菌在全身放疗的作用下被诱导移位至肠系膜淋巴结，再通过TLR4信号转导而增强ACT的疗效，给小鼠补充TLR4配体LPS同样可增强ACT的抗肿瘤反应。同样地，接受清髓性放疗预处理的转移性黑色素瘤患者对TIL过继治疗的效果更好[51]。近期研究[52]发现，ACT的疗效受肠道菌群的天然组成或抗生素治疗后导致的菌群改变或粪菌移植的显著影响。针对G^+菌的万古霉素可诱导全身性$CD8\alpha^+$ DC的增加，其以IL-12依赖性方式增强ACT的疗效[52]。这提示有望通过改变肠道菌群来改善ACT的疗效和肿瘤患者的预后。

3.2　对ICI疗效的影响

ICI是目前肿瘤免疫治疗的研究热点，表达于活化的T效应细胞表面的细胞毒性T淋巴细胞相关抗原4（cytotoxic T lymphocyte-associated antigen-4，CTLA-4）和程序性死亡受体1（programmed cell death protein-1, PD-1）及其配体1（PD-ligand 1, PD-L1）是重要的免疫负调控分子，可协助肿瘤细胞的免疫逃逸。

3.2.1　对CTLA-4抑制剂疗效和毒性的影响　无菌小鼠或抗生素治疗小鼠，其皮下肿瘤对抗CTLA-4抗体反应不佳。给予口饲多形拟杆菌或脆弱拟杆菌，可通过诱导肿瘤内DC成熟和肿瘤引流淋巴结的Th1应答，恢复对抗CTLA-4的治疗反应。用组合的脆弱拟杆菌和洋葱伯克霍尔德菌饲喂小鼠也能恢复对抗CTLA-4的治疗反应，通过过继转移脆弱拟杆菌特异性T细胞可恢复微生物贫化小鼠对抗CTLA-4的反应[53]。万古霉素通过减少G^+菌的丰度，同时保留G^-杆菌和伯克霍尔德菌，增强抗CTLA-4的抗癌疗效[53]。在抗CTLA-4治疗的患者中，肠道菌群中拟杆菌门的丰度增加与结肠炎的抗性相关，参与多胺转运和维生素B合成的细菌种类不足增加结肠炎发生风险[54]；脆弱拟杆菌和洋葱伯克霍尔德菌能显着降低与抗CTLA-4治疗相关的肠损伤程度[53]。不同基线肠道微生物群组成可影响机体的免疫治疗反应和免疫治疗相关不良反应的发生率。有研究[55]显示，其可作为预测伊匹单抗（ipilimumab）治疗的转移性黑素瘤患者临床反应和治疗相关结肠炎发生率的标志物，富含Faecalibacterium菌和厚壁菌门的基线肠道微生物群的患者使用伊匹单抗的临床反应更好，但治疗相关结肠炎的发生率更高。未来，需要开展多项研究比较微生物群与其他标志物对免疫治疗的预测价值，并在多种肿瘤和抗肿瘤综合治疗背景下深入研究。

3.2.2　对PD-1/L1抑制剂疗效的影响　肠道菌群种类及丰度对免疫治疗疗效产生重要影响。双歧杆菌属（短双歧杆菌、长双歧杆菌和青春双歧杆菌）可上调抗肿瘤相关基因的表达，影响DC成熟、抗原处理及提呈、$CD8^+$T细胞的活化和聚集、趋化因子介导的免疫细胞向肿瘤微环境的募集和Ⅰ型IFN信号转导等过程，增强抗肿瘤免疫应答。双歧杆菌联合PD-L1抑制剂，可增强$CD8^+$T细胞的活性，显著提高PD-L1抑制剂的抗肿瘤疗效[56]。有研究[57]发现，小鼠对PD-1/L1抑制剂的反应与艾克曼菌（Akkermansiamuciniphila，Akk）的相对丰度显著相关。将Akk菌通过口服或FMT给对PD-1/L1抑制剂治疗无效的小鼠，可通过诱导肿瘤组织内DC分泌IL-12，增加$CCR9^+CXCR3^+CD4^+Foxp3^+$T淋巴细胞向小鼠肿瘤床的募集，最终恢复PD-1抑制剂的疗效。研究[58]证实，定植于前列腺癌组织的大肠杆菌可下调肿瘤组织中VEGF的表达，上调肿瘤微环境中促炎细胞因子和趋化因子的表达，进而增加$CD8^+$T细胞、M1巨噬细胞等免疫细胞的浸润，并负性调控Treg细胞的数量，最终促使肿瘤细胞发生ICD。移植大肠杆菌与抗PD-1治疗相结合，显著增加原位MYC突变和PTEN突变前列腺癌模型的存活率并降低肿瘤负荷。

有研究者[59]通过对42例转移性黑色素瘤患者的粪菌构成进行分析发现，在对PD-1抑制剂疗效明显

的患者肠道菌群中存在高丰度的长双歧杆菌、产气柯林斯菌（Collinsella aerofaciens）和屎肠球菌；同样地，将这些菌群移植给无菌小鼠，能够显著增强肿瘤免疫应答和抑制肿瘤生长。而另一项对112例接受PD-1抑制剂的黑色素瘤患者的研究[60]表明，肠道菌群的多样性越丰富，抗PD-1治疗的疗效越好，患者PFS越长；在治疗有效的患者中，其肠道中梭菌属、瘤胃球菌、Faecalibacterium菌丰度更高，血液中有更多的$CD4^+$/$CD8^+$T细胞。在治疗无效的患者中，其肠道中多形拟杆菌、大肠杆菌和Anaerotruncus colihominis的丰度更高，其血液中Treg细胞和髓源性抑制细胞（myeloid-derived suppressor cell, MDSC）更多。这可能是因为在治疗有效患者肠道中发挥合成功能的细菌占优势，促进氨基酸合成，进而可能促进宿主免疫应答。

另外，免疫相关性肠炎是ICI的常见不良反应，已有应用FMT成功治愈难治性ICI相关性结肠炎的病例报道[61]。患者接受抗CTLA-4及抗PD-1治疗后出现重度结肠炎，但在接受FMT后，其肠道菌群得到重塑，Akk菌、双歧杆菌、布劳特氏菌（Blautia）丰度增加，肠道黏膜$CD4^+Foxp3^+$T细胞的比例相对增加，肠道炎症减轻、溃疡完全愈合[61]。未来，对FMT价值的探索有望治愈免疫相关性肠炎。

4 结 语

近年来，越来越多的证据表明肠道菌群可通过移位、参与信号转导、产生代谢酶、种类及丰度变化对化疗、放疗、免疫治疗产生重要影响，其主要临床结果有促进疗效、消除和减弱抗肿瘤作用、调节毒性等。未来，肠道菌群将在肿瘤的综合治疗中占有重要地位。肠道菌群或可作为预测肿瘤治疗疗效和毒副反应的生物标志物，有望成为抗肿瘤治疗过程中提高疗效和降低毒性的潜在应用方法。例如将有益菌群特异性的免疫细胞或细胞因子等活性成分应用于ACT；研制可应用于临床的药物代谢酶抑制剂阻止药物代谢所致的毒性及耐药；信号通路抑制剂可能改善治疗相关毒性；合理应用益生菌、FMT、有益菌群和特定抗生素来改善患者症状和预后。值得注意的是，一定要避免滥用抗生素以免对患者的抗肿瘤治疗产生负面影响。但目前尚存在诸多局限性：（1）目前的研究大多是在小鼠体内，不同研究得到的结果不完全一致，抗肿瘤药物在小鼠中的临床前分析可能受到不同种群中菌群组成的影响；（2）粪便菌群和肠道菌群存在差异[62]，因此在解释结果和应用到临床时须谨慎；（3）常用补充剂中的益生菌在人体肠道内定殖具有个体化差异[62-63]；（4）使用益生菌的不良反应尚未完全明确[64]；（5）肠道菌群种类繁多，作用复杂，被誉为“人类的第二基因组”。目前，人们对肿瘤患者的“微生物群-宿主-药物”相互作用的完整网络知之甚少，生物复杂性使得作用机制的深入探索存在困难。是否能发现既降低全身毒性又促进抗癌疗效的菌种或菌种组合，以及发现后如何在临床实践中对菌群进行个性化重塑以提高患者预后是我们面临的挑战。此外，关于“肿瘤靶向细菌”的研究也越来越多[65]，但何时能够得到临床转化尚需不断探索。未来，抗生素选择、补充益生菌和益生元、微生物移植等针对菌群的干预策略有可能成为肿瘤综合治疗的新手段。

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