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·综 述·

肠道菌群影响肿瘤对免疫检查点抑制剂的应答及其机制

Gut microbes influence response to immune checkpoint inhibitors and its mechanism

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[摘 要] 人类肠道菌群种类超过1 000种,是人体内最庞大的微生物群,被称为"被遗忘的器官"。肠道菌群易受多种因素影响。已有多项研究证明肠道菌群及其代谢产物参与宿主免疫构建和影响肿瘤微环境,与肿瘤对免疫检查点抑制剂(immune checkpoint inhibitor,ICI)的应答和ICI治疗相关不良反应的发生有关。随着人类微生物组计划的开展和测序分析技术的进步,肠道菌群的相关研究逐步深入,基因功能注释和代谢组学分析的成熟和推广丰富了肠道菌群与宿主免疫及免疫治疗间的探索维度,干预和塑造肠道菌群为提高肿瘤免疫治疗效果提供了新的思路。然而,微生物制品的食源性添加、粪菌移植等研究尚未获得足够证据,肠道菌群的免疫调控机制尚不完全清楚。本文就近年来肠道菌群影响肿瘤对ICI应答机制的研究进展作一综述。

[关键词] 肿瘤;免疫;免疫检查点抑制剂;粪菌移植;肠道菌群;代谢
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以CTLA-4、PD-1/PD-L1抑制剂为代表的免疫检查点抑制剂(immune checkpoint inhibitor,ICI),在黑色素瘤、非小细胞肺癌(non-small cell lung cancer, NSCLC)和肾细胞癌(renal cell carcinoma,RCC)等多种实体瘤的治疗中取得满意效果,然而其客观反应率(objective response rate,ORR)仅为25%[1]。目前认为,肿瘤对ICI的原发性耐药与肿瘤的突变负荷(tumor mutation burden,TMB)[2]、抗原提呈过程缺陷[3]、肿瘤免疫抑制微环境和肿瘤浸润淋巴细胞功能性耗竭等相关[4-5]。2015年,SIVAN等[6]报道,Jackson Laboratory(JAX)和Taconic Farms(TAC)来源的C57BL/6小鼠对ICI应答反应不一,且这种差异可以通过粪菌移植(fecal microbial transplantation,FMT)得以"矫正",肠道菌群与ICI的相关研究由此逐步开展。人类肠道菌群定植从出生时开始,至3岁左右完成,种类超过1 000种[7],是人体内最庞大的微生物群,以厚壁菌门(*Firmicutes*)、拟杆菌门(*Bacteroidetes*)和放线菌门(*Actinobacteria*)丰度最高[8-9]。肠道菌群参与人体消化、代谢,影响肠相关淋巴组织(gut-associated lymphoid tissues,GALT)的功能,并通过多种途径影响机体免疫[10-12],被称为"被遗忘的器官"。尽管已有多项高质量研究表明,肠道菌群影响宿主免疫应答,但其途径尚不完全清楚。本文就近年来肠道菌群影响肿瘤对ICI应答机制的研究进展作一综述。

1 肠道菌群影响宿主ICI应答

1.1 肠道菌群组成和抗生素应用影响宿主ICI应答

FRANKEL等[13]于2017年发表了首个关于人肠道菌群与ICI的前瞻性研究,对39例黑色素瘤患者粪菌行鸟枪测序法分析得出结论:ICI-R(response)组患者粪菌中粪拟杆菌(*Bacteroides caccae*)丰度高,而亚组分析则提示伊匹单抗(ipilimumab)+纳武单抗(nivolumab)联合R组与派姆单抗(pembrolizumab)单药R组患者粪菌富集菌不完全相同。GOPALAKRISHNAN等[14]对43例黑色素瘤患者粪菌群行16SrRNA测序分析发现,菌群α多样性是抗PD-1单克隆抗体临床获益的预测因素。HESHIKI等[15]对NSCLC、乳腺癌、结直肠癌(colorectal cancer,CRC)等8种不同类型肿瘤患者进行研究发现,肠道菌群特征是独立于肿瘤类型的,且健康人、ICI-R组和NR(non-response)组中观察到粪菌的β多样性逐渐降低,但是厚壁菌门/拟杆菌门比值逐渐升高。ROUTY等[16]对249例(NSCLC 140例、RCC67例、尿路上皮癌42例)接受抗PD-1/PD-L1单抗的肿瘤患者进行前瞻性队列研究发现,抗生素应用是ICI原发性耐药的独立危险因素(NSCLC:*HR*=2.31,95%CI=1.40~3.83,*P*<0.01;RCC:*HR*=2.16,95%CI=1.18~3.96, *P*<0.05)。将已报道的关于肿瘤患者肠道菌群与免疫治疗应答的研究汇总可以发现,不同研究报告的R组和NR组人群的"富集菌"仅存在轻微重叠(图1)。BHATT等[17]认为,各项研究纳入的患者群体的地理和饮食差异,以及测序及分析技术之间存在差异是不同研究报告的肠道菌群数据间差异的主要原因。

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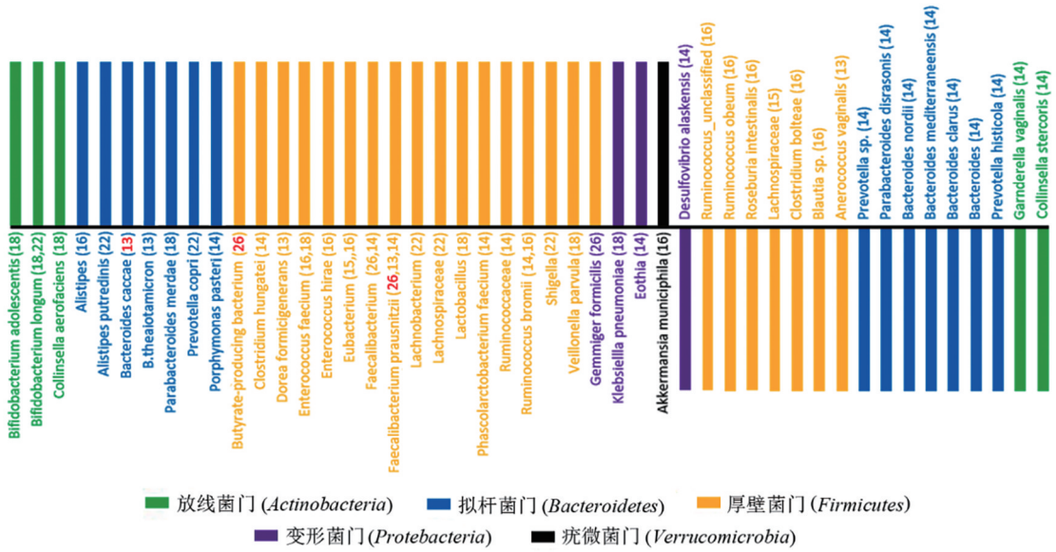

黑色横线上方的方条为ICI-R组富集的微生物，黑色横线下方的方条为ICI-NR组富集的微生物；括号内数字为参考文献的序号，红色数字为抗CTLA-4相关研究，其他颜色数字为抗PD-1/PD-L1相关研究

图1 肠道微生物影响肿瘤ICI应答的实验证据

1.2 菌群制剂和FMT影响宿主ICI应答

单一菌种的食源性添加有助于识别“有益菌”与“非有益菌”，FMT为肠道菌群影响肿瘤免疫应答提供直接证据。SIVAN等[6]研究证明食源性摄入双歧杆菌属（*Bifidobacterium*）活菌有助于减缓荷黑色素瘤小鼠肿瘤生长速度，但是小鼠粪菌群中梭菌目（*Clostridiales*）和产丁酸菌减少却与FMT中结果不一致。ROUTY等[16]研究报告，食源性添加嗜黏蛋白-艾克曼菌（*Akkermansia muciniphila*，*A.muciniphila*）可以改变荷瘤小鼠对ICI的应答状态。研究[18-19]证明，食源性添加*A.mucinipila*活菌并不能改变正常饮食组小鼠的肠道菌群分布。这些研究提示，双歧杆菌属和*A.mucinipila*等微生物不是通过调节肠道菌群丰度影响机体对ICI的免疫应答。近期，WANG等[20]的报告，饲喂巴氏灭活的*A.mucinpila*或外膜蛋白Amuc_1100对小鼠结肠炎相关的CRC也起到抑制作用，佐证了上述观点。JIN等[21]于2018年发表国内首个关于粪菌与肿瘤免疫治疗的研究，对43例应用nivolumab的NSCLC患者治疗过程中不同时点粪菌行16SrRNA测序发现，尽管R组和NR组人群的粪菌聚类分析明显分离，但在ICI治疗过程患者肠道菌群组成保持稳定，包括在疾病进展时，这与CHAPUT等[22]的研究结果一致。TANOUE等[23]选择最可能影响肿瘤免疫应答的11种微生物制成活菌混合制品，发现11种微生物是作为整体发挥作用的。HESHIKI等[15]用贝叶斯成分协方差分析（BAnOCC）法构建菌种网络图，发现NR组中共生梭菌（*Clostridium symbiosum*）和活泼瘤胃球菌（*Ruminococcus gnavus*）促使厚壁菌门成为优势菌，并驱逐拟杆菌门。上述研究不仅有力地证明菌群通过相互作用发挥调节功能，也表明单一菌种研究面临困境[24]。菌群组成的横向差异和纵向稳定将菌群对宿主的影响指向免疫调控，也成为FMT能够长期改善肿瘤免疫应答的重要前提。GOPALAKRISHNAN等[14]和ROUTY等[16]的研究都表明，接受R-FMT的无菌荷瘤小鼠对ICI产生更好的应答。2019年国际肿瘤免疫治疗会议上，来自以色列和美国的两个研究团队首次报告了免疫治疗未获益的黑色素瘤患者接受FMT后获益的研究[25]。

1.3 肠道菌群影响ICI治疗相关不良反应发生

除了治疗获益，ICI治疗相关不良反应（immune-related adverse event，irAE）也受到关注。多达3/4的接受ICI治疗者可能会发生irAE，主要累及皮肤、胃肠道、垂体、甲状腺、肝、心和肺等[26]。irAE的产生可能与自身反应性T细胞激活、免疫耐受降低、分子模拟和抗原播散有关，但具体机制尚不清楚[27]。有研究认为，个体肠道菌群的差异也与irAE的发生有关[22]，甚至可以作为irAE是否发生的预测标志物[28]。此外，应用FMT治疗ICI相关性结肠炎的病例已见报道[29-30]。这些研究提供了通过菌群调控宿主免疫，进而改善肿瘤患者免疫治疗获益和预测irAE的可能，然而菌群如何对宿主的免疫功能产生影响仍不完全清楚。

2 肠道菌群影响宿主免疫

2.1 肠道菌群影响宿主固有免疫

固有免疫是抵抗病原体侵入人体的第一道防

线，通过病原体相关模式分子（pathogen associated molecule pattern，PAMP）和模式识别受体（pattern recognition receptor，PRR）完成。从20世纪60年代无菌动物模型建立至今，肠道菌群在肠黏膜屏障和GALT发育和成熟中的作用被广泛探讨，其在髓系造血细胞分化和发育中的作用也逐渐引起关注。研究[31]表明，微生物依赖的免疫激活取决于小肠基底层CD11b$^+$树突状细胞（dendritic cell，DC）。FRANKEL等[13]发现，ICI-R组患者的粪菌微生物孵育的外周血单核细胞释放IFN-γ、IL-12的水平显著增高，意味着DC的激活[32]。革兰氏阴性菌粪拟杆菌、多形拟杆菌（*Bateroides thetaiotamicron*）、表面脂多糖（lipopolysaccharide，LPS）以TLR-4途径激活DC[33]，*A. muciniphila*和海氏肠球菌（*Enterococcus hirae*）也能诱导DC释放IL-12[16]。而VÉTIZOU等[31]对黑色素瘤和NSCLC荷瘤小鼠和患者的研究则提出，在肠道免疫耐受背景下，DC提呈脆弱拟杆菌（*Bacteroides fragils*）表面抗原，刺激IL-12依赖的记忆Th1细胞免疫应答并非通过TLR2/TLR4介导的固有免疫途径，而具体途径尚未阐明。DENG等[34]研究证明，脆弱拟杆菌能够诱导巨噬细胞表型向M1极化，并上调细胞表面CD80和CD86表达，增强抗肿瘤免疫。对17例NSCLC患者的研究[21]发现，外周血总NK细胞和PD-1$^+$GZMB$^+$NK细胞百分比与Shannon指数（代表菌群的多样性）显著相关。而DONG等[35]的研究证实，PD-L1$^+$NK细胞在ICI的作用下确有“增强的”抗肿瘤作用，意味着肠道菌群影响ICI治疗效果或许是通过调节NK细胞功能实现的。此外，肠道菌群可能通过影响奖励系统调控去甲肾上腺素能神经的输入[36]，抑制髓源抑制细胞（myeloid-derived suppressor cell，MDSC）的免疫抑制功能，从而影响抗肿瘤免疫[37]。然而，RUTKOWSKI等[38]的研究认为，肠道微生物可以通过TLR-5途径上调IL-6、动员MDSC，促进肿瘤生长。上述研究提示，肠道菌群激活的固有免疫并不总是对抗肿瘤有益的。

2.2　肠道菌群影响宿主适应性免疫

适应性免疫应答具有特异性、耐受性和记忆性，是指体内T、B淋巴细胞接受抗原刺激后，自身活化、增殖、分化为效应细胞，产生生物学效应的过程。适应性免疫应答，尤其是CD4$^+$ T细胞和CD8$^+$ T细胞，是抗肿瘤免疫的主要效应细胞，也是ICI作用的靶点[39]。

在自身免疫性疾病等的研究中发现肠道菌群能够影响CD4$^+$ T细胞向Treg细胞或Th17细胞的分化[40-44]。LI等[45]的研究显示，益生菌混合制剂Prohep治疗组的外周血、小肠和肿瘤浸润的Th17细胞都减少，认为肿瘤浸润的Th17细胞是通过循环系统从肠道中招募的。ROUTY等[16]采集27例NSCLC、28例RCC患者外周血单个核细胞与12种不同种微生物进行孵育，证明经*A.muciniphila*、海氏肠球菌孵育的自体单核细胞刺激CD4$^+$T细胞产生高水平IFN-γ与更好的无进展生存期（progression-free survival，PFS）获益相关；对荷瘤小鼠应用*A.muciniphila*、海氏肠球菌制剂后，在肠系膜淋巴结、肿瘤引流淋巴结及肿瘤浸润淋巴细胞中发现CD4$^+$ T细胞表达小肠相关性受体CCR9和Th1相关性受体CXCR3上调。GOPALAKRISHNAN等[14]对15例黑色素瘤患者行基线外周血流式细胞术检测发现，栖粪杆菌属（*Faecalibacterium*）、瘤胃菌科（*Ruminococcaceae*）、梭菌目高丰度者外周血CD4$^+$T、CD8$^+$T细胞数量更多，而拟杆菌目（*Bacteroidales*）高丰度者Treg细胞及MDSC数量更多。CHAPUT等[22]曾报道，拟杆菌门高丰度的黑色素瘤患者在接受CTLA-4抑制剂治疗时的结肠炎的发生率更低。DUBIN等[28]对34例接受CTLA-4抑制剂治疗的黑色素瘤患者的前瞻性研究也观察到相同的现象，并认为这与拟杆菌门诱导的Treg细胞分化有关，这也与LOUMA等[46]的观点一致。

SIVAN等[6]研究发现，双歧杆菌属活菌饲喂的荷瘤小鼠外周血中CD8$^+$T细胞功能增强且肿瘤组织中肿瘤特异性抗原阳性的CD8$^+$ T细胞比例增高。有研究[21]分析肠道菌群丰度和外周血免疫信号间的关系发现，在高丰度分类群中颗粒酶B（granzyme B，GrB）$^+$CD8$^+$Tm、Ki67$^+$CD8$^+$ Tm、CD8$^+$ Tcm在外周免疫系统中明显升高，意味着肠道菌群可能上调记忆T细胞的应答。TANOUE等[23]的研究显示，饲喂活菌并应用抗PD-1治疗的无菌荷瘤小鼠IFN-γ$^+$CD8$^+$ T细胞表达MC38肿瘤相关抗原p13E特异性的T细胞受体（TCR），且联合治疗导致GrB$^+$IFN-γ$^+$CD8$^+$T细胞和高表达MHC Ⅰ类分子的DC增加。上述研究表明，肠道菌群通过调控抗肿瘤效应细胞数量、重塑效应细胞对肿瘤相关抗原的识别和影响抗肿瘤效应细胞和免疫抑制细胞功能发挥免疫调控作用。

3　肠道菌群影响肿瘤免疫微环境

肿瘤的免疫抑制微环境被认为是原发性ICI耐药的原因之一，因此改善肿瘤微环境的免疫抑制性是提高抗肿瘤治疗疗效的重要途径。研究表明，接受抗PD-1单抗治疗R组患者基线期肿瘤组织CD8$^+$ T细胞密度更高[47-48]，而后者与栖粪杆菌属丰度、瘤胃菌科丰度正相关[14]。ROUTY等[16]发现，在接受抗PD-1单抗治疗时，同时接受经口灌胃补充*A.muciniphila*活菌的荷瘤小鼠肿瘤组织中CD4/Foxp3

比例更高。接受NR-FMT的无菌荷瘤小鼠肿瘤组织中RORγt$^+$ Th17细胞增多，与PD-1单抗无反应患者群中的结果一致[42]；而接受R-FMT的无菌荷瘤小鼠肿瘤组织中CD8$^+$ T细胞、CXCR3$^+$CD4$^+$ T细胞密度更高且肿瘤组织中PD-L1表达上调[49]。GOPALAKRISHNAN等[14]对黑色素瘤组织行免疫组织化学染色发现，相比于粪菌中拟杆菌目高丰度者（*n*=2），粪菌中栖粪杆菌属高丰度者（*n*=2）肿瘤组织中免疫细胞的数量和抗原提呈的分子标记表达更佳，提示肿瘤免疫抑制微环境的改善。

此外，肿瘤与炎性疾病不同的微环境为肠道菌群与免疫互作提供了更多的可能。CHAPUT等[22]曾报道，高丰度的厚壁菌门与ipilimumab更好的疗效和更严重的irAE相关。WANG等[20]的研究则发现，同样的微生物制剂在结肠炎小鼠模型中引起细胞毒性T淋巴细胞（cytotoxic T lymphocyte，CTL）表达PD-1的上调，但是在结肠癌模型中，PD-1$^+$CTL的比例却是降低的。尽管有“irAE的发生可能意味着更好的抗肿瘤疗效”的观点[50]，但严重的irAE会导致患者治疗中断甚至死亡，而这种相关性的强弱以及是否可以解除尚不清楚。基于炎症和肿瘤的不同微环境探索在改善肿瘤免疫应答的同时减少irAE的肠道菌群疗法将给肿瘤患者带来更大的获益。

4 菌群代谢产物影响宿主免疫应答

4.1 短链脂肪酸（short-chain fatty acid, SCFA）影响宿主免疫应答

随着肠道菌群相关研究的不断深入，“一个菌种，一种疾病”的理论显然不适用。代谢组学和蛋白质组学的应用给研究者提供了更多可探索的维度。多项研究证实，肠道菌群的代谢产物SCFA如丙酸、丁酸等能够促进肠上皮杯状细胞增殖，增强肠道屏障功能，减轻肠道微渗漏，使血清脂肪酶水平降低[19,51-52]，减少DC激活，降低全身基础炎症反应强度；此外，SCFA通过组蛋白去乙酰化酶（histone deacetylase，HDAC）[53]、转化生长因子-β1（transforming growth factor-β1，TGF-β1）[54]、G蛋白偶联受体43（G protein-coupled receptor 43，GPR43）[55]途径促进Treg细胞的产生和扩增，维持肠道局部的免疫耐受。SCFA在菌群调节的宿主抗肿瘤免疫应答中也备受关注。既往研究[56-59]显示，拟杆菌门能够发酵食物中的纤维，是肠道中SCFA的主要产生者。口服补充丁酸钠的CRC小鼠模型厚壁菌门/拟杆菌门比值降低，意味着菌群失调的改善，同时观察到肝中Th17细胞和NKT细胞增加和Treg细胞减少[60]。ZAGATO等[61]认为，小鼠肠道中的栖粪杆菌属*Rodentium*和人肠道中的对应微生物两歧霍尔德曼菌（*Holdemanella biformis*）产生SCFA，通过抑制钙调神经磷酸酶和活化T细胞核因子抑制肿瘤细胞增殖。另有研究[24,62]显示，不同微环境和宿主特异性因素可能导致SCFA产生不同的表型，这或许能够解释相同的微生物在不同的环境中表现出不完全一致的免疫调控功能。

4.2 其他影响宿主免疫应答的菌群代谢产物

NGUYEN等[63]对51 529例美国男性进行为期26年的随访发现，粪便中硫代谢菌群与CRC风险相关，且高硫微生物饮食者罹患远端CRC风险增加（*OR*=0.143，95%CI=1.14~1.81，*P*<0.05）。另有研究[64-66]表明，次级胆汁酸也可能是肠道菌群调控宿主免疫应答的中间桥梁，3β-羟基-脱氧胆酸（isoDCA）可作用于DC，抑制其免疫刺激作用，促进诱导外周Treg细胞[67]。FRANKEL等[13]对黑色素瘤患者粪菌行亚基因组鸟枪测序（metagenomic shotgun sequencing，MSS）发现，磷酸肌醇通路在ICI-R组中富集，而代谢组学分析则发现，在1 901种代谢产物中，腰果酸在ICI-R组显著增高（62倍，*P*<0.01）。既往的研究已经证实，磷酸肌醇可以调理中性粒细胞、NK细胞功能影响固有免疫，参与恶性肿瘤细胞的增殖、分化和凋亡的调控[68-69]；腰果酸通过MAP激酶和NF-κB磷酸化诱导巨噬细胞经典激活途径，从而激活固有免疫[70]，并通过诱导中性粒细胞胞外诱捕网（neutrophil extracellular trap，NET）形成影响肠道屏障，通过补体系统、T淋巴细胞等调控宿主适应性免疫[71-73]。有趣的是，在6例菌群代谢产物富含腰果酸的患者中，有5例患者有每周至少一次的腰果食用史，因此不能肯定R组患者肠道代谢产物中增加的腰果酸为菌群代谢产物或食源性摄入。TANOUE等[23]通过对比脾和肠的IFN-γ$^+$CD8$^+$T细胞的表型差异发现，系统免疫细胞不是细菌易位或菌群在肠道局部诱导产生的免疫细胞通过循环到达的，并认为是菌群代谢产物甲羟戊酸和二甲基乙二酰基甘氨酸引起系统的免疫应答。近期在CRC小鼠模型和患者来源的类器官模型上的研究[74]发现，补充α-酮戊二酸可以逆转低谷氨酰环境中Wnt信号的活化及干性增强，并促进细胞分化、抑制肿瘤生长和延长小鼠生存期。

此外，DUBIN等[28]认为研究中发现的拟杆菌门能够降低CTLA-4抑制剂治疗后发生ICI相关性结肠炎的风险与其参与肠道中水溶性维生素B生成[75-76]和多胺转运也有关，同时提出维生素B2、维生素B5、维生素B1和多胺转运系统的联合模型作为预测免疫治疗相关结肠炎的生物标志物（灵敏度70%，特异度83%）。应用代谢组学分析菌群代谢产物和免疫互作可能会为改善肿瘤患者的免疫应答和预测irAE提供

新的靶点。同时，应该注意以下两点：(1)肠道菌群的代谢产物受到饮食和药物等多种因素的影响，不同微生物间也存在严重的干扰，将相关成果进行临床转化还需要更多的研究证据；(2)膳食可以作为一种研究手段，但特定的膳食难以长期依附，因此很难作为一种治疗手段。

5 展　望

宏基因组学使肠道微生物群逐渐被人们认识。肠道菌群易受多种因素影响，各研究间应用菌群测序分析技术的差异、研究对象的地域差异等使得研究结果间可比性有限。但随着异质性研究的不断深入，菌群及其代谢产物在疾病中的角色逐渐清晰。肠道菌群中各菌种的共生和拮抗关系维系肠道微生物稳态，共同发挥对宿主的调控作用。抗生素使用影响肿瘤患者生存期的现象给患者的抗生素应用敲响了警钟，也有研究发现微生物制品等或可影响宿主免疫给肿瘤患者带来获益。Seres Therapeutics 公司根据动物实验和人体试验筛选出的“最能够影响免疫治疗应答”的微生物制品孢子粉已经在晚期黑色素瘤患者中开始试验[25]。目前国际上已开展的关于FMT和肿瘤免疫治疗疗效和不良反应的临床试验仅有7项：NCT03341143（黑色素瘤，*n*=20）、NCT03353402（黑色素瘤，*n*=40）、NCT04130763（胃肠道恶性肿瘤，*n*=5）、NCT04116775（前列腺癌，*n*=32）、NCT04264975（实体瘤，*n*=60）、NCT04163289（RCC，*n*=20）和NCT03819296（黑色素瘤，*n*=800），尚无结果呈现。尽管肠道菌群如何作用于人体系统免疫的机制尚不完全清楚，但现有研究提示肠道菌群可能是改善肿瘤免疫治疗疗效的潜在靶点，合理的抗生素选择、菌群调节剂的摄入和FMT的临床转化等手段为提高ICI的抗肿瘤疗效和减轻不良反应提供了新的可能，ICI联合菌群调控方案可能助力ICI获益人群的扩大。

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