肠道菌群调控提升免疫检查点抑制剂抗肿瘤效果研究进展

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摘要: 免疫检查点抑制剂 (immune checkpoint inhibitors, ICIs) 是癌症免疫治疗的重要药物, 但绝大部分患者对ICIs存在耐药性或短期反应。肠道菌群作为重要的免疫调节器, 已被证明在增强ICIs疗效中起关键作用。研究表明, 通过粪菌移植或特定菌株移植, 可直接改变肠道菌群的组成, 进而提升ICIs免疫治疗效果。此外, 饮食干预、益生元和后生元等手段也能通过调控肠道菌群提高ICIs的抗肿瘤效果。尽管如此, 如何优化菌群/株的选择和治疗方案仍需进一步探索。本文综述了肠道菌群调控在ICIs治疗癌症中的关键作用及其应用, 为提升肿瘤免疫治疗效果提供了实践基础和理论依据。

关键词: 癌症; 免疫治疗; 免疫检查点抑制剂; 肠道菌群; 粪菌移植

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Advance in gut microbiota regulation to enhance the anti-tumor efficacy of immune checkpoint inhibitors

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Abstract: Immune checkpoint inhibitors (ICIs) have emerged as critical agents in cancer immunotherapy; however, their resistance and limited response in most patients pose significant challenge. The gut microbiota, as a pivotal immune regulator, has been increasingly recognized for its role in enhancing the therapeutic efficacy of ICIs. Studies demonstrate that fecal microbiota transplantation or transplantation of specific bacterial strains can directly reshape the gut microbiota composition, thereby improving ICI therapeutic outcomes. Furthermore, dietary interventions, prebiotics, and postbiotics have shown potential in augmenting the anti-tumor effects of ICIs through gut microbiota modulation. Despite these promising findings, further investigations are required to optimize microbiota-based strategies and therapeutic protocols. This review highlights the critical role of gut microbiota modulation in ICI-based cancer therapy and explores its clinical applications, offering both practical insights and theoretical foundations for improving immunotherapy outcomes against various cancers.

Key words: cancer; immunotherapy; immune checkpoint inhibitor; gut microbiota; fecal microbiota transplantation

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癌症长期以来对人类健康构成重大威胁。癌症的常见治疗手段包括手术、放疗、化疗及免疫疗法等[1]，其中免疫疗法被《Science》杂志评为2013年十大科学突破之一[2]。作为一种新兴治疗策略，免疫疗法通过靶向激活宿主免疫系统进行治疗[2]。目前，免疫检查点阻断 (immune checkpoint blockade, ICB) 已成为抗肿瘤免疫疗法的主要策略之一[3]。肿瘤细胞通过激活免疫检查点途径“伪装”成正常组织细胞，从而逃避宿主免疫系统的监视[4,5]。在这些免疫检查点中，程序性细胞死亡受体1 (programmed cell death protein 1, PD-1) 及其配体程序性细胞死亡配体1 (programmed cell death ligand 1, PD-L1) 和细胞毒性T淋巴细胞相关抗原-4 (cytotoxic T-lymphocyte-associated protein 4, CTLA-4) 在维持T细胞的活化和免疫耐受功能中发挥着关键作用。因此，通过阻断PD-1/PD-L1和CTLA-4，免疫检查点抑制剂 (immune checkpoint inhibitors, ICIs) 为恢复免疫细胞的抗肿瘤活性和功能提供了新的途径[6]。ICIs的应用显著改善了多种癌症的临床预后，包括黑色素瘤、非小细胞肺癌 (non-small cell lung cancer, NSCLC)、肾细胞癌 (renal cell carcinoma, RCC)、胃癌、肝细胞癌和结直肠癌 (colorectal cancer, CRC) 等[7-9]。然而，绝大部分患者对ICIs表现出耐药性，或仅出现短暂的治疗反应，整体反应率较低 (约为10%～30%)[10-14]。

肠道微生物群作为一个整体存在于宿主体内，被认为是一个“超级器官”，其组成包括数万亿个共生微生物，如细菌、古细菌、病毒和真菌等[4]。肠道菌群作为肠道微生物群主要成员，其主要功能包括维持肠道健康、维持胃肠道屏障功能，以及膳食化合物和必需营养素的合成或转化等[15]。此外，肠道菌群在宿主免疫系统的发育与防御功能实现中也发挥着至关重要的作用[16,17]。在临床前研究和临床研究中，肠道菌群被公认为在调节局部及全身免疫反应方面具有重要作用[18-20]。2015年，两个独立研究发现肠道菌群能显著提高PD-L1抗体[21]和CTLA-4抗体[22]的肿瘤抑制效果，这一发现首次将肠道菌群与ICIs治疗联系了起来。随后的临床研究表明，抗生素处理与ICIs治疗效果呈负相关[23-26]，这进一步支持了肠道菌群完整性与ICIs抗肿瘤效果之间的密切关系。肠道菌群可以通过多种途径进行调节，如粪菌移植 (fecal microbiota transplantation, FMT)、特定菌株移植、饮食干预、益生元、抗生素、后生元及中药等，这些干预措施均有助于改善ICIs的疗效。本文将总结近年来关于肠道菌群调节对增强ICIs抗肿瘤效果的研究，包括临床前研究和临床试验的主要进展。

1 FMT增强ICIs的抗癌效果

鉴于肠道菌群的适应性特征，通过调节肠道菌群有望解决肿瘤患者对ICIs耐药性问题。FMT是一种常用的肠道菌群调节方法，通常采用口服冻干或冷冻胶囊，或通过结肠镜或胃镜将供体的粪便移植给受体[27]，从而调节宿主的肠道菌群稳态和免疫平衡[4]。

1.1 黑色素瘤

肠道菌群在ICIs发挥治疗作用的过程中发挥重要作用，重塑肠道菌群被认为是增强黑色素瘤患者对ICIs反应的重要策略。研究发现，TAC小鼠肠道菌群与JAX小鼠不同，且TAC小鼠接种黑色素瘤细胞后肿瘤生长较快。通过将JAX小鼠的粪便悬浮液与PD-L1抗体联合给药，发现这种联合方式显著抑制了TAC小鼠肿瘤生长，优于单独使用ICIs的疗法[21]。Vétizou等[22]分析了25例黑色素瘤患者在接受ipilimumab治疗前后的肠道微生物组成，识别出3个不同的微生物群聚类 (A、B和C类)。将具有不同微生物群聚类的患者的粪便样本移植到无菌小鼠体内，接种肿瘤并进行CTLA-4抗体处理。结果显示，移植C类患者粪便的小鼠表现出肿瘤生长抑制，而移植B类患者粪便则未产生明显抗肿瘤效应。此外，将PD-1抗体应答型黑色素瘤患者的粪便移植到无菌小鼠中，也可以改善肿瘤控制、增强T细胞应答，并提高PD-L1抗体的抗肿瘤效果[28,29]。这些研究进一步验证了通过肠道菌群调节可以增强ICIs的治疗效果。

两项里程碑式的FMT临床试验验证了FMT在增强PD-1抗体治疗肿瘤方面的有效性和安全性，显示出其在抗肿瘤联合治疗中的巨大潜力[30,31]。在第一项I期临床试验 (NCT03353402) 中，研究者对10例PD-1抗体难治性转移性黑色素瘤患者进行了FMT，评估了nivolumab再诱导的安全性与可行性。结果表明，3例患者获得了6个月以上的无进展生存期 (progression-free survival, PFS)，其中2例部分缓解 (partial responses, PR)，1例完全缓解 (complete responses, CR)。粪菌供体为接受nivolumab治疗后达CR超过1年的患者[30]。另一项II期临床试验 (NCT03341143) 评估了反应源性FMT联合PD-1抗体治疗在PD-1抗体难治性黑色素瘤患者中的安全性与有效性。结果显示，15例患者中有6例表现出临床治疗效果，其中1例CR，2例PRs，3例病情稳定 (stable disease, SD) 超过一年，并引发了持续的微生物群扰动[31]。这两项研究表明，FMT联合PD-1阻断能够改善肠道菌群，重编程肿瘤微环境，并通过调节局部和全身免疫反应逆转PD-1抗体的耐药性，为治疗难治性黑色素瘤提供了新的方案。

随后，研究人员评估了健康供体FMT联合ICIs在

未经治疗的黑色素瘤患者中的疗效。一项I期临床试验 (NCT03772899) 评估了健康供体FMT与PD-1抗体联合治疗晚期黑色素瘤的效果。结果显示, 65%的患者 (20例中有13例) 获得了客观缓解, 其中包括4例CRs。此外, Avatar小鼠模型进一步证实了健康供体粪便在提高抗PD-1疗效中的作用[32]。另一项II期临床试验 (NCT04951583) 报告了健康供体FMT与PD-1抗体/CTLA-4抗体联合治疗晚期黑色素瘤患者的结果。该研究纳入20例黑色素瘤患者, 结果显示75%的患者 (4例CRs) 获得了客观缓解[33]。这两项研究表明, 来自健康供体的FMT在临床试验中是安全且有效的。鉴于招募患者供体的限制, 使用健康供体的粪便制备FMT胶囊为此类研究提供了一种安全且可行的选择[32]。

1.2　非小细胞肺癌

为研究肠道菌群在提升ICIs抗肿瘤效果中的关键作用, 将来自不同NSCLC患者 (4例ICIs应答者和4例无应答者) 的粪便移植到8只SPF条件下饲养的抗生素处理小鼠 (或无菌小鼠) 体内[25]。对小鼠接种MCA205肿瘤细胞后, 小鼠再接受PD-1抗体处理。实验结果显示, 来自应答者的FMT小鼠肿瘤生长受到明显抑制, 而来自无应答者的FMT小鼠表现出PD-1抗体耐药性。另一项研究则从65例接受ICIs治疗的NSCLC患者中收集粪便样本, 将应答者和无应答者的肠道菌群分别移植到肺癌悉生小鼠中, 并进行ICIs治疗。结果表明, 应答者的肠道菌群能显著提高ICIs抑制肿瘤生长的效果[34]。为了表征肠道菌群的多样性和组成及其与ICIs应答的关系, 研究人员对71例晚期NSCLC患者接受ICB治疗前的粪便样本进行了分析, 并将不同患者的粪便移植到小鼠体内评估PD-1抗体的治疗效果。结果显示, 肠道菌群多样性的提升与ICIs治疗反应之间存在显著相关性; 来自应答者和无应答者的FMT与PD-1联合均能抑制小鼠肿瘤的生长[35]。此外, 一些临床试验 (如NCT05008861和NCT04924374) 已经评估了FMT联合ICIs对NSCLC患者的安全性和有效性, 尽管这些试验结果没有正式公布。

1.3　肾细胞癌

Routy等[25]将来自7名RCC患者的粪菌移植到经抗生素处理的BALB/C小鼠体内, 随后植入对PD-1抗体耐药的荧光素酶标记的肾癌细胞, 并用CTLA-4抗体和PD-1抗体进行联合治疗。实验数据显示, 来自应答患者的粪便样品恢复了CTLA-4和PD-1联合阻断的抗肿瘤活性, 而无应答患者的粪便则未显示此效应。在一项II期临床试验 (NCT03013335) 中, 69名接受nivolumab治疗的RCC患者被纳入研究。研究发现, 抗生素的使用显著降低了患者对nivolumab的反应率 (从28%降至9%)。与健康供体相比, RCC患者的微生物群组成发生了明显变化。来自应答RCC患者的粪菌能补偿接受无应答患者粪菌的小鼠的耐药性, 从而改善PD-1抗体的肿瘤治疗效果[36]。

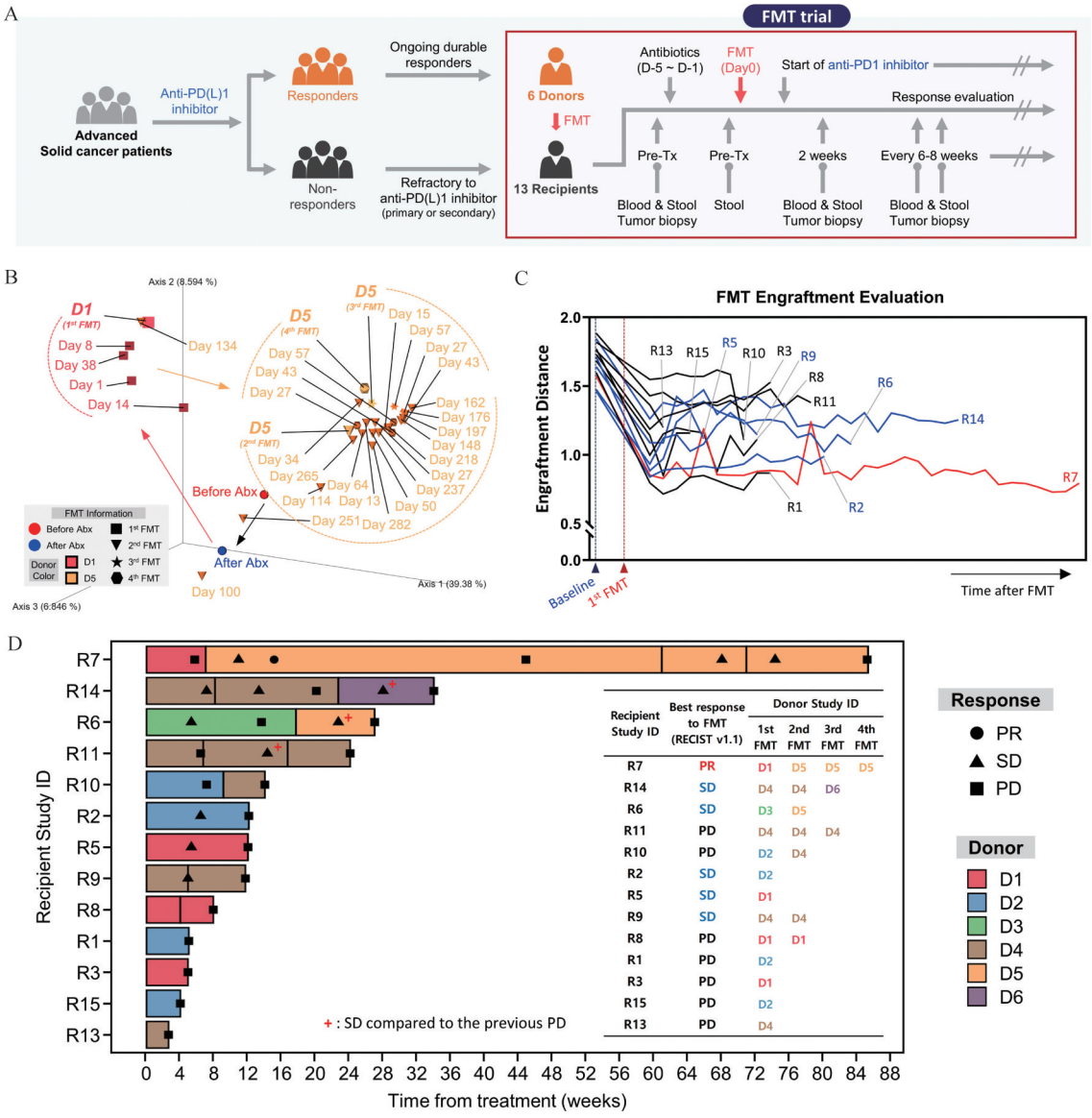
临床试验 (NCT04163289) 评估了FMT与免疫疗法联合治疗一线转移性RCC的安全性, 并探讨FMT是否能够预防或减轻免疫相关不良事件 (immune-related adverse events, irAEs)。10例患者接受了FMT和双重ICIs治疗, 其中8例患者发生了irAEs。4/9的患者获得了客观缓解, 其中1例为PR[37]。另一项II期随机临床试验 (NCT04758507) 评估了来自ICIs应答者的FMT在提高转移性RCC患者对pembrolizumab和axitinib联合治疗的效果。结果显示FMT组1年PFS为66.7%, 客观缓解率为54.0%, 显著高于安慰剂组[38]。

1.4　胃肠道癌症

与单独使用PD-1抗体处理的小鼠相比, FMT联合PD-1抗体治疗显著提高了CRC荷瘤小鼠的存活率和肿瘤抑制效果。宏基因组分析表明, 联合治疗的小鼠肠道菌群发生了明显变化, 特别是拟杆菌属[39]。微卫星稳定 (microsatellite stabilization, MSS) 转移性CRC (metastasis CRC, mCRC) 通常对PD-1抑制剂反应较差。在一项II期试验 (ChiCTR2100046768) 中, MSS mCRC患者接受了FMT联合tislelizumab和fruquintinib作为三线或以上治疗。结果表明, FMT联合tislelizumab和fruquintinib在既往标准治疗策略失败的难治性MSS mCRC患者中显示出良好的抗肿瘤效果和可接受的安全性[40]。

一项临床试验 (NCT04264975) 评估了来自PD-1抗体应答者的FMT联合PD-1抑制剂治疗13例ICIs难治性转移性胃肠道肿瘤患者。结果显示, 6例患者的肠道菌群发生了持续变化, 并在该临床试验中获益, 其中1例PR, 5例SDs, 客观缓解率为7.7%, 疾病控制率为46.2% (图1[41])。为进一步探讨健康供体FMT是否能克服PD-1抗体在胃肠道肿瘤中的耐药性, 一项开放标签、单组临床研究 (NCT04130763) 评估了FMT联合nivolumab治疗PD-1抗体耐药/难治性胃肠道癌症患者的疗效。结果表明, nivolumab + FMT联合治疗的耐受性良好, 无严重不良反应发生。应答者的肠道菌群组成更接近于健康供体, 且其α多样性明显高于无应答者[42]。

除了上述癌症类型, FMT联合ICIs在其他癌症治疗中的研究也取得了进展, 如胶质母细胞瘤[43]、肝细胞癌 (NCT05690048、NCT05750030)、间皮瘤 (NCT04056026) 和前列腺癌 (NCT04116775)。这些临床前小鼠模型和临床试验 (表1[30-33,37,38,40-42,44,45]) 表明, FMT能够调节恶



Recipient Study ID	Best response to FMT (RECIST v1.1)	Donor Study ID 1st FMT	2nd FMT	3rd FMT	4th FMT
R7	PR	D1	D5	D5	D5
R14	SD	D4	D4	D6	
R6	SD	D3	D5		
R11	PD	D4	D4	D4	
R10	PD	D2	D4		
R2	SD	D2			
R5	SD	D1			
R9	SD	D4	D4		
R8	PD	D1	D1		
R1	PD	D2			
R3	PD	D1			
R15	PD	D2			
R13	PD	D4			

Figure 1 Clinical response of FMT combined with nivolumab in patients with nivolumab-refractory advanced solid tumors[41]. A: Schematic of FMT combined with anti-PD-1/PD-LI inhibitors in the treatment of patients with resistance to anti-PD-1/PD-L1; B: Beta diversity analysis (Bray-Curtis dissimilarity) of R7 patients before and after FMT; C: FMT engraftment evaluation using engraftment distance (ED); D: Clinical data of FMT recipients. FMT: Fecal microbiota transplantation; PD-1: Programmed cell death protein 1; PD-L1: Programmed cell death ligand 1; PD: Progressive disease. Reprinted with the permission from Ref.41. Copyright © 2024 Elsevier

性肿瘤患者对ICIs的敏感性, 验证了FMT联合ICIs治疗的有效性和安全性, 并进一步支持通过调节肠道菌群来增强肿瘤免疫治疗的概念。然而, 由于致病菌、寄生虫、噬菌体及多重耐药细菌可能在不被察觉的情况下通过粪便传播, 因此在进行FMT时, 研究人员必须高度谨慎[18]。

2 特定菌株移植增强ICIs的抗癌效果

FMT通过将供体的整个肠道菌群移植到受体体内, 直接重建肠道菌群[46,47]。不仅如此, 特定菌株移植(单一菌株或菌株联合体)也能直接调节肠道菌群, 从而增强ICIs的肿瘤免疫治疗效果(表2[48-55])。

2.1 单一菌株移植增强ICIs的抗癌效果

2.1.1 益生菌 益生菌是一类有益的活性微生物, 对肠道菌群具有广泛的积极影响, 可作为癌症免疫治疗的协同药物, 在激活免疫系统、抑制肿瘤生长方面发挥关键作用[56]。益生菌不仅能够调节肠道菌群和免疫反应, 影响机体对ICIs的反应, 还可以定向转运至肿瘤部位并发挥抗肿瘤作用[57-59]。

Bifidobacterium 属包含多种益生菌, 广泛应用于肠道健康产品中。一项基于4T1三阴性乳腺癌的临床

Table 1 Clinical trials of the combination of FMT and ICIs for cancer treatment. ICIs: Immune checkpoint inhibitors; ICB: Immune checkpoint blockade; NSCLC: Non-small cell lung cancer; RCC: Renal cell carcinoma; CRC: Colorectal cancer; HCC: Hepatocellular carcinoma; PR: Partial response; CR: Complete response; ORR: Objective response rate; PFS: Progression-free survival; DCR: Disease control rate; CBR: Clinical benefit rate; SD: Stable diseases; irAEs: Immune-related adverse events

FMT source	Disease	Model	ICI	Enrollment	Key result	Reference
Nivolumab responders	Melanoma	Patients with metastatic melanoma refractory to anti-PD-1	Nivolumab	40	Two PRs and one CR in 10 patients	NCT03353402[30]
Nivolumab or pembrolizumab responders	Melanoma	Patients with anti-PD-1 refractory melanoma	Pembrolizumab	18	Well tolerated; clinical benefit was achieved in 6 of 15 patients; rapid and persistent microbiota perturbations	NCT03341143[31]
Healthy people	Melanoma	Treatment-naïve patients with advanced melanoma	Anti-PD-1	20	Two patients had a vigorous immune response to FMT; one patient experienced several grade 2 toxicities with stabilization of a large cutaneous lesion; ORR was 65% (13 of 20), including 4 CRs	NCT03772899[32,44]
Anti-PD-1 responders	Melanoma	ICI refractory patients	ICIs	5	Not stated	NCT04577729
MaaT013, a microbiome restoration biotherapeutic	Melanoma	Patients with unresectable or metastatic melanoma	Ipilimumab and nivolumab	60	Ongoing	NCT04988841
ICI responders or non-responders	Melanoma	Anti-PD-1-refractory patients with advanced stage cutaneous melanoma	Anti-PD-1	24	Ongoing	NCT05251389
ICI responders	Melanoma	Patients with PD-1 relapsed/refractory cutaneous melanoma	Pembrolizumab	56	Ongoing	NCT06030037
FMT selected according to the abundance of bacterial taxa in the feces	NSCLC	Stage III/V NSCLC naïve for PD-1/PD-L1 inhibitors	Anti-PD-1	25	Not stated	NCT04924374
Not stated	NSCLC	Patients with locally advanced or metastatic NSCLC after first-line treatment with anti-PD-1/PD-L1	Anti-PD-1/PD-L1	20	Not stated	NCT05008861
Anti-PD-1 responders	NSCLC	Patients with relapsed/refractory PD-L1 positive NSCLC	Pembrolizumab	26	Ongoing	NCT05669846
Immunotherapy responders	Lung cancer	Patients with metastatic lung cancer	Immuno-oncology	80	Ongoing	NCT05502913
Healthy people	RCC	Patients with untreated advanced or metastatic RCC	Nivolumab and ipilimumab	20	ORR was confirmed in 4/9 patients; 1 PR	NCT04163289[37]
ICI responders	RCC	Patients with metastatic RCC	Pembrolizumab	50	One-year PFS rate was 66.7%; ORR was 54%	NCT04758507[38]
Healthy people	Gastrointestinal cancer	Patients with anti-PD-1 resistant/refractory gastrointestinal cancer	Nivolumab	10	Nivolumab + FMT therapy was well tolerated	NCT04130763[42]

Continued

FMT source	Disease	Model	ICI	Enrollment	Key result	Reference
FMT capsules XBI-302	Gastric cancer	Patients with anti-PD-1/PD-L1 resistant gastric cancer	Nivolumab	0	Not stated	NCT05001360
Not stated	CRC	Patients with refractory microsatellite stable metastatic CRC	Tislelizumab	20	ORR was 20%; DCR was 95%; CBR was 60%	ChiCTR2100046768[40]
Not stated	CRC	CRC patients with advanced stages	Sintilimab	30	Not stated	NCT05279677
Anti-PD-1 responders	CRC	Anti-PD-1 non-responders with metastatic CRC	Pembrolizumab, nivolumab	15	Ongoing	NCT04729322
Not stated	HCC	Patients with advanced HCC	Atezolizumab, bevacizumab	48	Ongoing	NCT05690048
Anti-PD-1/PD-L1 responders	HCC	Patients with HCC who failed to respond to atezolizumab/bevacizumab	Atezolizumab and bevacizumab	12	Ongoing	NCT05750030
Anti-PD-1 responders	Solid cancer	Patients with anti-PD-1-refractory advanced solid cancers	Anti-PD-1	60	FMT induced clinical benefits in 6 of 13 patients, with 1 PR and 5 SDs, achieving an ORR of 7.7% and a DCR of 46.2%	NCT04264975[41]
Anti-PD-1/PD-L1 responders or non-responders	Solid cancer	Patients with advanced, unresectable, or metastatic solid cancer who have progressed during anti-PD-1/PD-L1 therapy	Nivolumab	50	Ongoing	NCT05533983
Pembrolizumab responders	Prostate cancer	Patients with metastatic castration-resistant prostate cancer	Pembrolizumab	32	Not stated	NCT04116775
Healthy people	Mesothelioma	Patients with metastatic mesothelioma	Anti-PD-1	1	Not stated	NCT04056026
Healthy people	NSCLC/melanoma	Unresectable or metastatic NSCLC/melanoma	Pembrolizumab, ipilimumab and nivolumab	20/20	In the NSCLC cohort, there were no grade ≥ 3 irAEs; in the melanoma cohort, ORR was 75% (4 patients in CR)	NCT04951583[33]
ICI responders	Melanoma, microsatellite instability-high/mismatch-repair deficient cancer or NSCLC	Adult subjects with treatment-refractory or inoperable cancer	Nivolumab	42	Not stated	NCT04521075
ICI responders	Melanoma, cutaneous squamous cell carcinoma, head and neck squamous cell carcinoma, renal clear cell carcinoma, NSCLC and micro-satellite instability high solid cancers	Patients with progressive disease on ICI therapy	ICIs	20	Five patients (56%) have recorded SD and 4 patients (44%) progressive disease	NCT05286294[45]
ICI responders	Malignancy	Patients with refractory malignancy	Cancer immunotherapies	18	Not stated	NCT05273255

Table 2 Clinical application of specific strains, dietary interventions, prebiotics, and postbiotics in ICI-based cancer treatment

Intervention	Disease	Model	ICI	Enrollment	Key result	Reference
Single bacteria						
CBM588	RCC	Treatment-naïve patients with metastatic RCC	Nivolumab and ipilimumab	30	PFS was significantly longer	NCT03829111[48]
CBM588	RCC	Locally advanced or metastatic RCC	Nivolumab	30	ORR was 74% and PFS was 84%	NCT05122546[49]
EDP1503	CRC	Patients with metastatic microsatellite instability CRC	Pembrolizumab	32	Combination therapy was safe and well tolerated	NCT03775850[50]
EDP1503	Melanoma	Patients with advanced melanoma	Pembrolizumab	8	Ongoing	NCT03595683
MRx0518	Solid cancer	Patients with solid tumors who have progressed on PD-1 inhibitors	Pembrolizumab	63	Not stated	NCT03637803
GEN-001	Solid cancer	Patients with solid tumors who have progressed on anti-PD-1/PD-L1 therapy	Avelumab	11	Not stated	NCT04601402
Lactobacillus Bifidobacterium V9 (Kex02)	NSCLC	Karnofsky score ≥ 90 in patients receiving immunotherapy for NSCLC	Carilizumab	46	Not stated	NCT05094167
Lactobacillus rhamnosus Probio-M9	Liver cancer	Karnofsky score ≥ 90 in patients receiving immunotherapy for liver cancer	Anti-PD-1	46	Not stated	NCT05032014
Bacterial consortium						
BMC128	NSCLC-adenocarcinoma, ccRCC and cutaneous melanoma	Patients progressed on PD-1/PD-L1 inhibitors	Nivolumab	12	Four out of the first 8 patients in the study showed SD and sustained benefit beyond the first imaging timepoint	NCT05354102[51]
SER-401	Melanoma	Patients with advanced melanoma	Nivolumab	14	In the vancomycin+SER-401/nivolumab arm, ORR was 25.0% and DCR was 37.5%	NCT03817125[52]
MET4	Solid cancer	Locally-advanced or metastatic solid malignancy which is incurable	ICIs	65	The trial achieved its primary safety and tolerability outcomes	NCT03686202[53]
VE800	Advanced or metastatic cancer	Patients with anti-PD-1/PD-L1 relapsed/refractory melanoma, naïve gastric/gastroesophageal junction adenocarcinoma and naïve microsatellite-stable CRC	Nivolumab	56	Not stated	NCT04208958
Live combined (*Bifidobacterium*, *Lactobacillus* and *Enterococcus* Capsules)	Urothelial bladder carcinoma	Patients with urothelial carcinoma and undergoing immunotherapy	Cancer immunotherapies	190	Ongoing	NCT05220124
Diet interventions and prebiotics						
High-fiber diet	Melanoma	Patients with melanoma	Nivolumab and ipilimumab	71 Australian and 32 Dutch patients	Increase the abundance of Ruminococcaceae, improve the anti-tumor immune response, and reduce the risk of irAEs during immunotherapy	NCT02977052[54]
High-fiber diet	Melanoma	Melanoma patients starting ICB	ICB	50	The interventions were well-tolerated	NCT04645680[55]

Continued

Intervention	Disease	Model	ICI	Enrollment	Key result	Reference
Potato starch	Solid tumor	Patients undergoing cancer treatment with a dual ICIs for solid cancer	Ipilimumab and nivolumab	12	Not stated	NCT04552418
Ketogenic diet	RCC	Patients with metastatic RCC	Nivolumab and ipilimumab	60	Not stated	NCT05119010
Fasting-mimicking diet	Solid or hematologic malignancy	Patients with different cancer types	Nivolumab, pembrolizumab	90	Not stated	NCT03595540
Fasting-mimicking diet	NSCLC	Patients with advanced NSCLC	Pembrolizumab	12	Not stated	NCT03700437
Camu camu	RCC	Patients with kidney cancer that has spread to other places in the body	Nivolumab and ipilimumab	30	Ongoing	NCT06049576
High-fiber, plant-based diet + exercise	Melanoma	Adults with melanoma	Ipilimumab and nivolumab, relatlimab and nivolumab, pembrolizumab, or nivolumab	80	Ongoing	NCT04866810
Low-protein diet (10% protein content)	Solid tumor malignancies	Cancer patients receiving immunotherapies	ICIs	30	Ongoing	NCT05356182
Postbiotics						
MS-20	NSCLC	Metastatic stage IV NSCLC	Pembrolizumab	30	Not stated	NCT04909034

前研究表明, *Bifidobacterium longum* RAPO与PD-1抗体联合能够增强抗肿瘤免疫应答[60]。对96例NSCLC患者肠道微生物组的分析发现, *Bifidobacterium bifidum* (*B. bifidum*) 在具有良好治疗反应性的患者的肠道中含量较高。特定的*B. bifidum*菌株能够通过激发抗肿瘤宿主免疫反应, 在治疗同源小鼠肿瘤时与PD-1阻断剂联用, 可显著抑制肿瘤的生长[61]。此外, 一项随机I期试验 (NCT03829111) 研究了双歧活菌产物CBM588联合nivolumab和ipilimumab免疫疗法对转移性RCC患者的影响。该试验结果显示, 接受联合治疗患者的PFS和疾病缓解率明显优于未接受CBM588治疗的患者 (12.7个月 *vs* 2.5个月), 从而证明了CBM588能提高RCC患者对免疫治疗药物的临床响应[48]。*Lactobacillus*属是另一类常见的益生菌。Bender等[59]发现*Lactobacillus reuteri*能自发迁移到黑色素瘤中并定殖, 释放膳食色氨酸衍生代谢物吲哚-3-乙醛, 依赖于AhR受体局部促进能产生干扰素γ (interferon-γ, IFN-γ) 的$CD8^+$ T细胞杀死肿瘤细胞, 从而增强ICIs的抗肿瘤效果。*Lactobacillus rhamnosus* GG (LGG) 是一种被广泛应用的益生菌。在小鼠CRC和黑色素瘤模型中, 口服LGG可诱导树突状细胞 (dendritic cells, DCs) 产生干扰素β, 通过增加肿瘤浸润性DCs和T细胞的数量来增强PD-1抗体的抗肿瘤活性[62]。

研究表明, 补充益生菌*Lacticaseibacillus rhamnosus* Probio-M9可以重塑肠道微生态, 并调节代谢途径增强PD-1抗体的免疫反应, 从而显著提高肿瘤抑制效果[58,63] (图2)。*Clostridium butyricum*与接受ICIs治疗的晚期或复发性NSCLC患者的良好预后相关[64], 补充该菌株可显著延长PFS和总生存期[65]。同样, 补充*Lactococcus lactis* GEN3013可增加肿瘤微环境中细胞毒性免疫细胞群的比例, 增强PD-1阻断剂的抗肿瘤效果[66]。此外, 工程益生菌的开发也取得了进展。Canale等[67]利用合成生物学技术开发了一种工程化益生菌*Escherichia coli* (*E. coli*) Nissle 1917株, 能定植于肿瘤组织深部并持续将氨转化为*L*-精氨酸, 从而增加肿瘤内T细胞浸润。*E. coli* Nissle 1917与PD-L1抗体联合使用时, 可显著提升肿瘤清除效果。

这些研究表明, 益生菌补充可与ICIs协同作用, 增强免疫治疗的效果和耐受性, 具有广阔的应用前景。

2.1.2 其他有益菌株 除了已经定义的益生菌外, 其他有益菌株也能增强ICIs的抗肿瘤效果。*Akkermansia muciniphila* (*A. muciniphila*) 与NSCLS和RCC的良好临床免疫治疗结果相关。接受抗生素处理的小鼠和接受无反应患者FMT的小鼠在口服*A. muciniphila*后, 均恢复了对PD-1抗体的响应性[25]。此外, *Eubacterium rectale*通过抑制*L*-丝氨酸的合成, 显著增加了自然杀伤细胞的活化, 从而提高了PD-1抗体的疗效[68]。对接

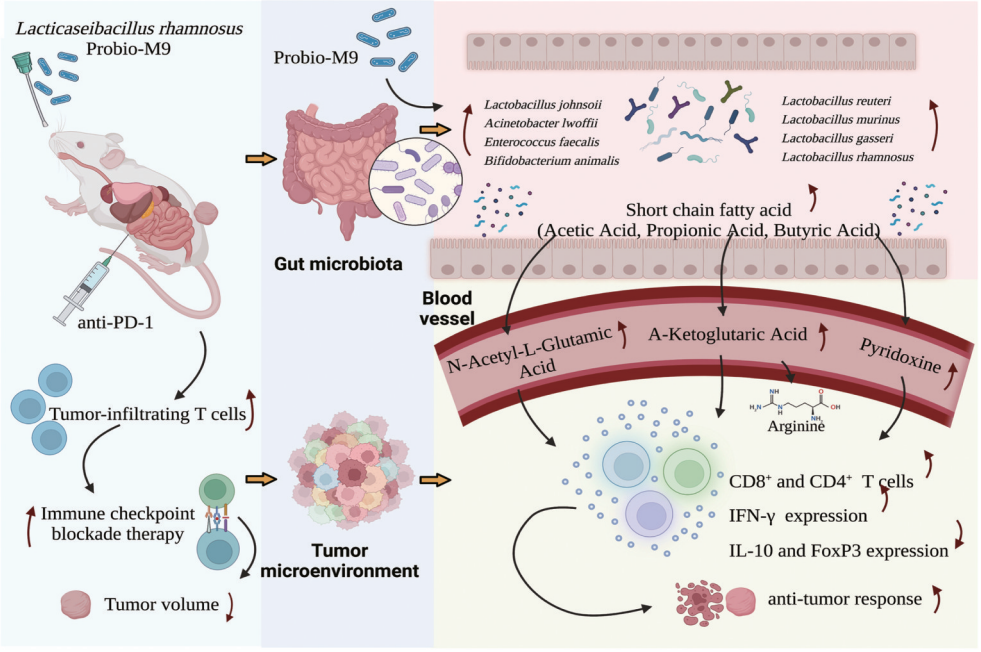


Figure 2　Schematic of oral supplementation with *Lacticaseibacillus rhamnosus* Probio-M9 to enhance the efficacy of anti-PD-1 immunotherapy[58]. IFN-*γ*: Interferon-*γ*; IL-10: Interleukin-10; FoxP3: Forkhead box protein P3. Reprinted with the permission from Ref.58. Copyright © 2023 Elsevier

受PD-1免疫疗法有反应的人群中, 共生微生物组中*Enterococcus*属丰富。与单独使用PD-L1抗体治疗的黑色素瘤小鼠相比, 补充人类共生*Enterococcus faecium* (*E. faecium*) Com15菌株可进一步提高PD-L1抗体抑制肿瘤生长的效果, 后续的研究揭示了该协同治疗效果与*E. faecium* Com15分泌NlpC/p60肽聚糖水解酶SagA的同源物有关[69]。*Coprobacillus cateniformis*单定殖无菌小鼠, 通过抑制肠系膜淋巴结和肿瘤引流淋巴结中DC表面PD-L2的表达, 提高肿瘤对PD-L1抗体的免疫应答水平[70]。补充*Bacteroides fragilis*可触发DC成熟和刺激IL-12依赖性Th1细胞免疫反应, 以增强CTLA-4抗体的治疗效果[22,71]。*Faecalibacterium prausnitzii*已被证实具有免疫调节作用, 该菌株可改善ICIs引发的结肠炎, 重塑肠道微生物组成, 并增强ICIs的抗肿瘤免疫反应[72]。

此外, 有研究发现在不同癌症类型的ICIs应答者中, 几种微生物物种持续富集, 包括细菌和真核生物[73]。与单独补充细菌的黑色素瘤或非小细胞肺癌小鼠相比, *Faecalibacterium prausnitzii*或*Coprococcus comes*与PD-1抗体治疗联合使用可进一步减轻肿瘤重量和缩小肿瘤体积。同样, 真核生物*Nemania serpens*或*Hyphopichia pseudoburtonii*与PD-1抗体联合使用, 也能显著降低肿瘤的生长速率。该研究不仅验证了细菌在ICIs治疗中的关键作用, 还揭示了真核生物作为ICIs反应预测因子的潜力, 具有重要的临床意义。*Fusobacterium nucleatum* (Fn)是一种革兰阴性厌氧菌, 被认为是CRC的重要致病病原体[74]。研究发现, Fn的丰度与CRC患者PD-1阻断治疗反应的改善相关[75]。实验数据显示, Fn通过激活STING信号通路在增强肿瘤对PD-L1抗体敏感性中起关键作用。最近的报道揭示, Fn通过丁酸依赖途径提高MSS CRC小鼠对PD-1抗体的敏感性[76]。这些结果表明某些致病菌可能在肿瘤发生和免疫治疗过程中产生不一致的影响。

综上, 补充特定有益菌株可以调节免疫系统, 增强ICIs的抗肿瘤效果, 为癌症免疫治疗提供新的策略。遗憾的是, 补充单一菌株可能会破坏肠道菌群作为一个平衡整体的多样性[77], 未来仍需对该策略进行系统深入的研究。

2.2　菌株联合体移植增强ICIs的抗癌效果

Tanoue等[71]从健康人群供体粪便中分离出一个由11种菌株组成的联合体 (7个拟杆菌门和4个非拟杆菌门), 这些菌株能够在肠道中诱导大量的IFN-*γ*分泌型$CD8^+$ T细胞。该11种菌株联合体定殖于CRC小鼠后, 能通过$CD8^+$ T细胞依赖形式有效增强自发和ICIs介导的抗肿瘤免疫反应。一项针对黑色素瘤小鼠的临床前研究表明, 口服双歧杆菌混合物 (*Bifidobacterium breve*和*Bifidobacterium longum*) 能显著增强PD-L1抗体的肿瘤抑制效果, 几乎彻底抑制肿瘤的生长[21]。此外, 有研究表明口服4种梭菌混合物可以有效预防和

抑制CRC, 在CRC和黑色素瘤小鼠模型中显著增强PD-1抗体的肿瘤抑制效果[78]。

在一项早期临床试验 (NCT03686202) 中, MET4 (包含30种微生物的联合体) 联合ICIs在对晚期实体瘤患者展开治疗的过程中, 表现出良好的安全性和耐受性。在联合治疗组中, 有1例CR, 7例PRs, 6例SDs[53]。在另一项临床评估试验 (NCT03817125) 中, SER-401 (一种细菌联合候选药物) 与nivolumab联合治疗14例一线转移性黑色素瘤患者。研究表明SER-401和PD-1抗体的联合使用具有良好的安全性, 但与对照组相比, vancomycin+SER-401/nivolumab组的抗肿瘤效果降低, 这可能与抗生素的使用有关[52]。

总之, 以上研究证实了菌株联合体作为癌症免疫治疗的潜在辅助手段的可行性。菌株联合体不仅有效地减少了FMT过程中携带致病菌或耐药菌的风险, 还解决了单一菌株可能引起肠道菌群失衡的问题。然而, 微生物干预的最佳菌株、剂量和持续时间仍需要广泛的研究。

3 其他肠道菌群干预手段提高ICIs抗癌效果

除了FMT和特定菌株移植直接调控肠道菌群之外, 饮食调节、益生元、后益元、抗菌药物及中药等策略也能有效改变肠道菌群的组成, 从而改善ICIs的免疫治疗反应。

3.1 饮食调节和益生元

鉴于饮食对肠道菌群具有显著影响, 饮食干预作为一种通过调节肠道菌群来提高免疫治疗效果的潜在策略, 引起了广泛关注[27]。Ferrere等[79]研究表明, 生酮饮食通过其主要酮体3-羟基丁酸盐介导的抗肿瘤作用, 依赖T细胞介导的免疫监视, 呈现抑制肿瘤生长和增强ICB疗效的潜力。一项临床研究 (NCT05119010) 正在进行中, 旨在评估生酮饮食或酮补充剂联合nivolumab和ipilimumab治疗转移性RCC患者的效果。高纤维饮食可通过增加肠道菌群的α多样性, 改善肿瘤对PD-1抗体的敏感性。研究表明, 具有良好肠道菌群和高纤维饮食的患者对PD-1抗体免疫治疗的应答率是低纤维饮食患者的5倍[80]。Lam等[81]发现, 高纤维饮食通过调节肠道菌群激活肿瘤内IFN-I-NK-DC轴, 重塑肿瘤微环境, 从而增强ICB疗效。同样的, 摄入高膳食纤维与接受ICIs治疗的黑色素瘤患者PFS的改善显著相关, 尤其是那些未使用益生菌的患者[55]。在接受新辅助ICIs治疗的转移性黑色素瘤患者中, 高纤维饮食增加了瘤胃球菌科的丰度, 并促进了抗肿瘤免疫反应[54]。饮食干预具有良好的安全性、可及性和低成本, 是调节患者肠道菌群的一种简单方法[82]。总的来说, 这些研究有望揭示饮食干预作为癌症免疫治疗辅助手段的潜在益处, 从而为改善患者预后提供了更多选择。

益生元是一类非活性的食品补充剂, 包含不可消化的食物成分, 能够选择性促进肠道特定有益微生物的生长[83]。大多数益生元属于膳食纤维[84]。食用益生元被认为是一种安全且非侵入性的调节肠道菌群的方法[85]。菊粉是一种常见的膳食纤维。研究表明, 菊粉凝胶经口服后可以滞留于结肠组织表面, 能有效调节小鼠肿瘤模型的肠道菌群, 诱导系统性记忆T细胞反应, 并增强PD-1抗体的抗肿瘤活性 (图3[86])。与健康对照组相比, CRC患者肠道菌群人源化荷瘤小鼠对PD-1抗体敏感性显著降低, 而果胶补充能显著增强PD-1抗体的肿瘤抑制效果[87]。研究发现, 口服超细红枣粉可改变肠道菌群, 增加*Clostridiales*属的丰度和提高短链脂肪酸 (short-chain fatty acids, SCFAs) 的生产, 促进$CD8^+$ T细胞向肿瘤微环境的浸润, 并显著提高PD-L1抗体治疗结肠腺癌的效果[88]。

3.2 后生元

后生元是由微生物代谢活动释放或产生的物质, 通常包括肽类、酶、抗菌肽、多糖和代谢物等, 这些物质通过直接或间接作用对宿主产生有益影响[89]。与活菌药物相比, 后生元更为安全, 并对宿主健康具有多种益处。

SCFAs是肠道菌群 (如瘤胃球菌科、乳杆菌科和双歧杆菌科等) 通过发酵不可消化的食物纤维和糖蛋白产生的代谢产物[90-92]。有研究表明, SCFAs (如乙酸、丙酸、丁酸和戊酸等) 能改善ICIs的临床抗肿瘤效果。粪便中SCFAs浓度的升高与PD-1抗体免疫治疗的长期疗效及更长的PFS相关[93,94]。进一步研究表明, 联合给予肠道微生物来源的SCFAs (如乙酸盐) 和PD-1抗体可增强肝脏肿瘤抑制效果[92]。

此外, 经口补充细菌来源的代谢物去氨酪氨酸可有效抑制肿瘤的生长, 并提高CTLA-4抗体或PD-1抗体的免疫治疗效果[95]。胰腺导管腺癌 (pancreatic ductal adenocarcinoma, PDAC) 是一种难治性肿瘤。研究发现肠道菌群衍生的代谢物氧化三甲胺与ICIs联合使用, 可显著降低PDAC小鼠模型肿瘤生长速率, 并提高了荷瘤小鼠生存率[96]。MS-20, 一种含有丰富微生物代谢物的后生元, 与PD-1抗体的联合用于异种移植小鼠模型, 能显著抑制结肠癌和肺癌的生长[97]。Kawanabe-Matsuda等[98]发现微生物*Lactobacillus delbrueckii subsp. bulgaricus* OLL1073R-1产生的外多糖 (EPS-R1), 能诱导小鼠和人类产生大量$CCR6^+CD8^+$ T细胞。EPS-R1的摄入可提高$CCR6^+CD8^+$ T细胞在肿瘤组织中的浸润量, 刺激其分泌大量IFN-γ, 并增强

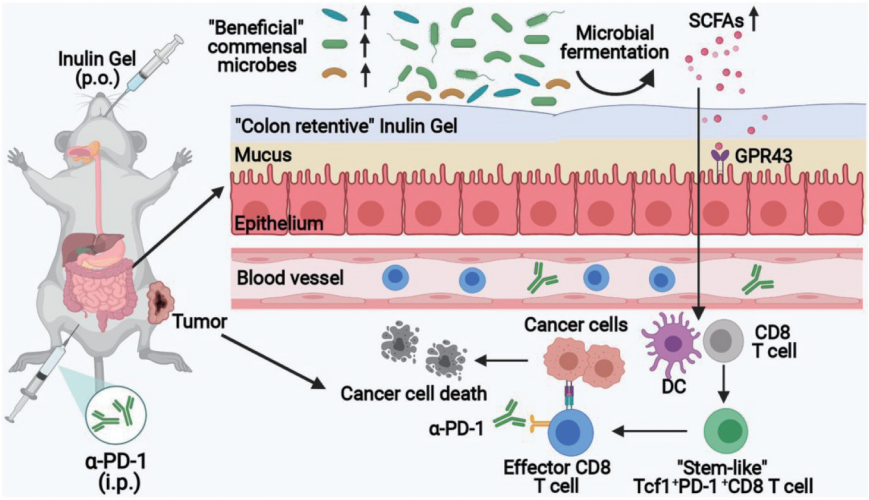


Figure 3　Schematic of "colon-retentive" inulin gel for *in situ* modulation of the gut microbiome to enhance the efficacy of anti-PD-1 immunotherapy[86]. SCFAs: Short-chain fatty acids; GPR43: G-protein coupled receptor 43. Reprinted with the permission from Ref. 86. Copyright © 2021 Springer Nature

CTLA-4 抗体或 PD-1 抗体对表达 CCL20 肿瘤细胞的生长抑制效果。

细菌胞外囊泡 (extracellular vesicles, EVs) 含有大量的生物活性蛋白、脂质、核酸和代谢物等, 是细菌与细菌、细菌与宿主相互作用的重要介质。研究表明, 细菌 EVs 通过多种机制调节免疫反应, 因此在增强 ICIs 抗肿瘤作用方面具有重要的应用潜力[99]。

3.3　抗生素

根据抗菌谱, 抗生素可以用来消除损害 ICIs 抗肿瘤效果的细菌[85]。在癌症患者中, 抗生素通常用于预防和治疗一系列可能危及生命的感染, 这些感染可能使癌症治疗复杂化[91]。研究表明, 口服万古霉素可增加革兰阴性菌的丰度, 同时减少革兰阳性菌的丰度, 提高 CTLA-4 拮抗剂对荷瘤小鼠的肿瘤抑制效果[22]。Pushalkar 等[100]发现, 与正常小鼠和人类的胰腺相比, 癌变胰腺中的菌群更为丰富。口服抗生素可提升胰腺癌患者对 ICIs 的疗效。他们认为胰腺瘤内菌群产生了免疫抑制微环境, 用抗生素消除瘤内菌群可增强机体产生抗肿瘤免疫反应。事实上, 晚期癌症患者接受 ICIs 治疗时, 广谱抗生素治疗会导致较低的缓解率和较差的 PFS, 而窄谱抗生素的使用则不产生显著影响[24]。一项包括 48 项研究的系统综述和荟萃分析也表明抗生素的使用对总生存期、无进展生存期和治疗反应率等有负面影响[101]。这些相互矛盾的发现表明抗生素对 ICIs 疗效的影响是不确定的, 需要进一步的研究来确定如何更好地给将要接受或正在接受 ICIs 治疗的患者施用抗生素, 包括最佳时机、持续时间和抗生素类型[91]。

3.4　中药单体及处方

多项研究表明, 中医药及单体不仅能够调节肠道菌群[102], 还能作为肿瘤免疫微环境的调节剂, 促进抗肿瘤免疫应答[85]。Lv 等[103]发现, 葛根芩连汤 (Gegen Qinlian Decoction, GQD) 与 PD-1 抗体联合使用时, 在小鼠异种移植模型中对结肠肿瘤具有明显的抑制作用。GQD 和 PD-1 抗体联合使用可显著改变肠道菌群, 同时提高外周血和肿瘤组织中 $CD8^+$ T 细胞的比例, 提高 IFN-γ 的合成并下调 PD-1 的表达。此外, 研究表明参龄白术汤可能通过增加肠道菌群多样性, 提高肿瘤微环境中 M1 型巨噬细胞的比例, 同时减少 M2 型巨噬细胞和 Treg 细胞的数量, 从而与 tirelizumab 联合协同治疗 CRC[104]。薯蓣皂苷元是一种天然甾体皂苷, 可通过调节免疫功能和改善肠道菌群来发挥抗肿瘤作用。薯蓣皂苷元与 PD-1 抗体联用可通过富集 *Lactobacillus* 和 *Sutterella* 以及下调 *Bacteroides* 的丰度, 增强 T 细胞反应, 从而抑制 B16-F10 荷瘤小鼠的肿瘤生长[105]。

4　微生物群调控增强 ICIs 抗癌机制研究

大量证据表明, 肠道菌群在提升 ICIs 治疗效果方面起着至关重要的作用。肠道菌群通过多种机制提高 ICIs 免疫治疗的效果, 包括激活模式识别受体的微生物相关或病原相关分子模式 (如脂多糖)、肠道菌群代谢物 (如 SCFAs、肌苷和胆汁酸)、细菌易位, 以及自身抗原与微生物异种抗原的交叉反应性[6]。研究人员发现, 活性 enterococci 通过表达并分泌 NlpC/p60 肽聚糖水解酶 SagA 的直系同源物, 产生具有免疫活性的胞壁肽。胞壁肽依赖天然免疫传感器核苷酸结合寡聚结构

域 2 (nucleotide-binding oligomerization domain 2, NOD2), 增强 PD-L1 抗体的肿瘤抑制效果[69]。此外, *Bifidobacterium pseudolongum* 主要通过肠道微生物代谢物肌苷促进 Th1 转录分化和抗肿瘤免疫应答, 从而提高 ICI 疗效。肌苷的作用取决于 T 细胞腺苷 A_{2A} 受体的表达[106]。Choi 等[107]发现 ICB 诱导淋巴结重塑和 DC 激活, 从而诱导特定内源性肠道细菌易位到次级淋巴器官和皮下黑色素瘤肿瘤中, 进一步促进肿瘤引流淋巴结和皮下肿瘤的抗肿瘤 T 细胞反应。一项研究发现共生菌 *Bifidobacterium breve* 表达抗原 SVY, 靶向 SVY 的 T 细胞与黑色素瘤 B16 表达的新抗原 SIY 发生交叉反应, 表明共生细菌可以通过交叉反应来刺激抗肿瘤免疫反应[108]。研究表明, 肠道菌群在癌症免疫周期的多个环节中发挥作用, 包括癌症抗原的呈递与 T 细胞的启动/激活、T 细胞的肿瘤转运与浸润, 以及 T 细胞对肿瘤抗原的识别与细胞毒性作用[109]。为了开发更精确且个性化的肠道菌群调控策略, 仍需深入研究特定菌群及其代谢物如何与宿主免疫细胞互作的具体细胞与分子机制[110]。

5 总结与展望

近年来, 以 ICIs 为代表的肿瘤免疫治疗技术得到了广泛关注, 肠道菌群在调节免疫反应及提升肿瘤治疗效果方面发挥着重要作用。本文综述了多项临床前和临床研究, 重点探讨了肠道菌群在增强 ICIs 抗肿瘤治疗效果中的潜力。结合肠道菌群的治疗策略, 如 FMT、特定菌株植入、饮食干预、益生元、后生元及中药等, 为将肠道菌群作为 ICIs 治疗的有效辅助手段奠定了基础。

总体而言, 基于菌群调控与 ICI 的联合治疗的临床试验仍处于初期阶段。目前的临床结果表明, 肠道菌群在促进 ICI 治疗反应方面具有良好的安全性和有效性。然而, 肠道菌群相关生物标志物具有明显异质性。鉴于研究条件的差异, 异质性可归因于癌症类型、应答者定义、粪便样本收集与储存、测序技术、下游生物信息学分析、队列规模及地理差异等因素[111]。目前, 仍未能筛查出能在多种肿瘤类型中提升 ICIs 疗效的“超级肠道菌群”[4]。因此, 建议开展更大规模的宏基因组分析, 涵盖不同种族群体并控制潜在的混杂因素, 同时结合多学科方向分析关键微生物以及深入研究肠道菌群与 ICIs 之间复杂的互作机制。FMT 存在传播潜在有害或具有致癌潜力微生物群的风险[112]。在 ICI 治疗的背景下, FMT 的未来发展至关重要, 需要有标准化的 FMT 方案, 包括 FMT 供体的选择; FMT 的分离、纯化与储存标准; FMT 治疗程序; 抗生素的使用等。补充单一菌株被认为是“窄谱”微生物疗法, 可能会破坏肠道菌群平衡[77]。有研究表明, 非处方益生菌可能对接受 ICI 治疗的癌症患者的预后有不利影响, 并且与较低水平的微生物多样性和较低的应答率相关[55]。未来, 基于个体肠道菌群组成的精准调节有望成为新的治疗策略。专注于特定细菌的应用可有效减少使用整个 FMT 时可能转移病原体的风险, 并且还可以提供一致的治疗产品。同时, 未来肠道菌群疗法应侧重于特定功能而非单一物种的存在, 以提高 ICIs 治疗的安全性和有效性。

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