•综述•

靶向肠道菌群改善肿瘤免疫治疗耐药策略的研究进展

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摘要: 越来越多的研究指出, 肠道菌群在肿瘤免疫治疗中扮演着关键角色。通过优化肠道菌群的组成, 可以有效改善免疫治疗耐药性并增强其治疗效果。本文综合分析了肠道菌群失调介导肿瘤免疫治疗耐药机制, 阐述了当前采用的中药和植物成分、粪便菌群移植、益生菌、益生元和饮食疗法等靶向调节肠道菌群策略, 探讨了这些策略改善患者对肿瘤免疫治疗耐药性的潜在机制。同时, 文章还简要讨论了靶向肠道菌群改善肿瘤免疫治疗耐药性的前景与挑战, 为相关研究提供了参考, 以助力逆转肿瘤免疫治疗耐药的策略研究。

关键词: 肠道菌群; 肿瘤免疫治疗; 靶向调节; 改善耐药机制; 应用挑战

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Research progress on strategies to target intestinal microbiota to improve drug resistance in tumor immunotherapy

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Abstract: A growing body of research points out that gut microbiota plays a key role in tumor immunotherapy. By optimizing the composition of intestinal microbiota, it is possible to effectively improve immunotherapy resistance and enhance its therapeutic effect. This article comprehensively analyzes the mechanism of intestinal microbiota influencing tumor immunotherapy resistance, expounds the current strategies for targeted regulation of intestinal microbiota, such as traditional Chinese medicine and plant components, fecal microbiota transplantation, probiotics, prebiotics and dietary therapy, and explores the potential mechanisms of these strategies to improve patients' resistance to tumor immunotherapy. At the same time, the article also briefly discusses the prospects and challenges of targeting intestinal microbiota to improve tumor immunotherapy resistance, which provides a reference for related research to help the strategy research of reversing tumor immunotherapy resistance.

Key words: intestinal microbiota; tumor immunotherapy; targeted regulation; improve drug resistance mechanism; application challenge

近年来, 免疫治疗已成为肿瘤治疗的重要组成部分。然而, 耐药性的出现是当前免疫治疗面临的重大挑战。越来越多的证据表明, 肠道菌群在结直肠癌 (colorectal cancer, CRC)、非小细胞肺癌 (non-small cell lung cancer, NSCLC)、胃癌和肝癌患者的免疫治疗反应中起着重要作用, 肠道菌群的组成和稳态对免疫治

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疗的敏感性有密切联系[1-4]。Jin等[5]对37例接受纳武利尤单抗治疗的晚期NSCLC患者的研究中发现, 对程序性死亡受体1 (programmed cell death protein 1, PD-1)单抗有反应的患者在治疗开始时肠道菌群多样性更高, 治疗期间肠道菌群组成更稳定, 患者无进展生存期显著延长, 长双歧杆菌和普氏双歧杆菌的富集与更好的免疫治疗反应和疗效相关。然而, 肠道菌群失调会影响免疫治疗效果, 使肿瘤细胞对治疗产生耐药性, 从而影响患者治疗效果。肿瘤、炎症等则会引起肠道微生态紊乱, 偶氮甲烷/葡聚糖硫酸钠诱导的结肠炎相关肿瘤小鼠模型的早期阶段, 肠道普雷沃氏菌科增加和厌氧原体科减少, 可以持久过度刺激CD8 T细胞导致T细胞耗竭, 干扰免疫系统发挥作用, 从而介导免疫治疗耐药[6]。靶向肠道菌群调节, 维持肠道微环境稳态, 有助于提高肿瘤免疫治疗成功率。研究表明, 中药及植物成分、粪便微生物群移植 (fecal microbiota transplantation, FMT)、益生菌、益生元、饮食疗法等措施都会调节肠道菌群组成和稳态而改善肿瘤免疫治疗耐药[7-10]。本文概述了肠道菌群失调介导肿瘤免疫治疗耐药的机制和通过调节肠道菌群逆转肿瘤免疫治疗耐药的策略及改善耐药的机制, 并分析了靶向肠道菌群在肿瘤免疫治疗耐药中的机遇和挑战。

1 肠道菌群失调介导肿瘤免疫治疗耐药的机制

近年来的研究表明, 肠道菌群的组成及其代谢产物可以影响包括免疫检查点抑制剂 (immune checkpoint inhibitors, ICIs) 等免疫治疗的疗效。研究发现, 短期或长期使用抗生素与肿瘤免疫治疗耐药之间存在关联, 抗生素治疗引起的肠道菌群紊乱会减弱ICIs在多种肿瘤类型 (黑色素瘤、非小细胞肺癌、透明细胞肾细胞癌、鳞状细胞癌等) 中的疗效, 接受ICIs治疗前30天进行抗生素治疗导致患者对ICIs治疗反应差、生存期缩短[11-13]。不同抗生素处理的CT26荷瘤小鼠肠道菌群组成和各菌属丰度存在差异, 且广谱类抗生素组对PD-1单抗无反应, 黏菌素组对PD-1单抗反应较差, 万古霉素组对PD-1单抗反应中等, 对照组反应良好。其潜在机制可能由抗生素治疗引起肠道菌群变化, 进一步影响体内甘油磷脂的代谢和鞘糖脂生物合成, 下调肿瘤微环境中干扰素γ (interferon-γ, IFN-γ) 和白介素-2 (interleukin-2, IL-2) 表达, 从而导致PD-1单抗的治疗效果较差[14]。

肠道菌群产生的代谢产物已被证实在一定程度上能够削弱ICIs治疗效果。这些代谢物通过与人体免疫系统的复杂相互作用, 可能会对ICIs的疗效产生负面影响。肠道菌属具核梭杆菌产生的琥珀酸可激活琥珀酸受体1 (succinate receptor 1, SUCNR1)-缺氧诱导因子1α (hypoxia-inducible factor 1 alpha, HIF-1α)-zeste基因增强子同源物2 (zeste homolog 2, EZH2) 轴, 从而损害环状GMP-AMP合酶 (cyclic GMP-AMP synthase, cGAS)-干扰素β (interferon-β, IFN-β) 通路, 并减少肿瘤中的Th1型趋化因子CCL5和CXCL10, 限制CD8 T细胞募集到肿瘤微环境, 降低结直肠癌中PD-1阻断治疗的抗肿瘤应答[15]。肠道菌群*Firmicutes*和*Bacteroidetes*将初级胆汁酸转化为次级胆汁酸, 这一转化过程降低肝窦内皮细胞中CXCL16的表达, 减少肝脏$CXCR6^+$自然杀伤T细胞的积累, 促进肝癌细胞的增殖[16]。乙酸是肠道菌群代谢物短链脂肪酸 (short chain fatty acids, SCFAs) 的一种, NSCLC细胞对乙酸摄取增加了乙酰辅酶A的合成。二氢硫辛酰胺转乙酰基酶 (dihydrolipoamide *S*-acetyltransferase, DLAT) 具有蛋白质乙酰转移酶的功能。而DLAT则利用乙酰辅酶A提供的酰基对原癌基因c-Myc Lys148位点进行了乙酰化修饰。该位点的修饰被去泛素化酶10识别, 促进了其对c-Myc的去泛素化, 维持了c-Myc的稳定性, 随后转录了编码PD-L1、糖酵解酶和促细胞周期的基因, 减弱CD8 T细胞浸润来促进免疫抑制肿瘤微环境的形成[17]。肠道菌群来源的色氨酸可以被吲哚胺2,3-双加氧酶1和色氨酸2,3-双加氧酶2催化, 沿犬尿氨酸途径分解代谢, 产生犬尿氨酸等代谢产物。这些代谢产物能够结合并激活免疫细胞上的芳烃受体, 导致一系列生物学效应, 包括诱导调节性T细胞 (regulatory T cells, Tregs) 的生成、促进树突细胞和巨噬细胞向免疫抑制表型的转化, 从而抑制免疫反应[18]。

这些研究结果表明, 抗生素使用和肠道菌群代谢产物通过多种机制影响ICIs的疗效, 这些机制包括影响免疫细胞的募集、激活和功能, 以及调节肿瘤微环境中的代谢和信号传导途径 (表1)。因此, 维持肠道菌群的平衡对于优化免疫治疗的效果至关重要。

2 靶向肠道菌群改善肿瘤免疫治疗耐药的调节策略

基于靶向肠道菌群调节以改善肿瘤免疫治疗耐药性是一个充满潜力的新兴领域。目前, 已经有一些策略在临床前和临床研究中显示出了积极效果, 如中药及植物成分、靶向特定肠道菌群移植、益生菌、益生元和饮食疗法等帮助恢复或增强肠道中有益菌群, 提高免疫治疗疗效[19], 调节策略见表2。

2.1 中药和植物成分基于肠道菌群组成和代谢物改善肿瘤免疫治疗耐药 最近研究表明, 中药和植物成分可以重塑肠道菌群结构和代谢, 调节免疫细胞功能和细胞因子释放, 改善肿瘤免疫微环境的组成, 并显示出将“冷”肿瘤 (即免疫沙漠) 转化为“热”肿瘤 (即免疫浸润) 的潜力, 降低肿瘤免疫治疗耐药性发生, 以增强

Table 1 Mechanism of intestinal microbiota mediated immunotherapy resistance

Mechanism of resistance section	Immunotherapy resistance factor	Gut microbiota mediates mechanisms of drug resistance
Mechanisms of intestinal dysbiosis mediating tumor immunotherapy resistance	Antibiotics	It causes intestinal flora disorder, affects lipid metabolism and immune factor expression *in vivo*, and reduces the efficacy of PD-1 monoclonal antibody
	Intestinal bacteria have succinic acid derived from *Fusobacterium nucleata*	Succinic acid activates the SUCNR1-HIF-1α-EZH2 pathway, inhibits the cGAS-IFN-β pathway, reduces Th1 chemokines, restricts CD8 T cells, and reduces the efficacy of PD-1 blocking therapy for colorectal cancer
	Bile acids derived from the intestinal flora	The intestinal microbiota converts primary bile acids into secondary bile acids, reduces the expression of CXCL16 in hepatic sinusoidal endothelial cells, and then reduces the accumulation of $CXCR6^+$ natural killer T cells in the liver and promotes the proliferation of hepatocellular carcinoma cells
	Acetic acid derived from the intestinal flora	Acetate increases intracellular acetyl-CoA in NSCLC, acetylates c-Myc protein through dihydrolipoamide *S*-acetyltransferase, is recognized by deubiquitinase 10, stabilizes c-Myc, promotes PD-L1 expression and glycolysis, inhibits CD8 T cells, and forms an immunosuppressive tumor microenvironment
	Tryptophan of intestinal flora-derivation	The intestinal flora metabolizes tryptophan to produce kynurenine, which activates aryl hydrocarbon receptors on immune cells, promotes Tregs production and immunosuppressive cell transformation, and inhibits immune responses

Table 2 Regulatory strategies for improving immunotherapy resistance based on intestinal microbiota

Regulation strategy section		Targeted regulation of intestinal flora	Improving the mechanism of drug resistance based on the regulation of intestinal microbiota
Traditional Chinese medicine and botanical components improve tumor immunotherapy resistance based on intestinal microbiota composition and metabolites	Astragalus polysaccharides	*Bifidobacterium pseudolongum*, *Lactobacillus johnsonii*, *Lactobacillu* and other intestinal flora abundance increases	It causes an increase in metabolites such as glutamate and creatine, reduces the expression of immunosuppressive cells MDSCs and their related molecules, inhibits tumor growth, and enables CD8 T cells to kill tumor cells more effectively
	Baicalin	*Akkermansia* and *Clostridia_UCG-014* were significantly increased, and caproic acid, butyric acid and valeric acid in SCFAs were significantly increased	SCFAs enhance CD8 T cells in the tumor microenvironment, promote TNF-α and IFN-γ secretion, reduce Tregs inhibition, and improve anti-PD-1 therapy resistance
	Ginseng polysaccharides	The abundances of *Bacteroides vulgatus* and *Parabacteroides distasonis* and the metabolite valeric acid of intestinal flora increased, while the content of immunosuppressive metabolite *L*-kynurenine and the proportion of kynurenine tryptophan decreased	The increase of valeric acid and the decrease of kynurenine metabolites in the intestinal microbiota can help to increase the ratio of CD8/CD4 T cells, enhance the ability of CD8 T cells to secrete IFN-γ, TNF-α and GZMB, and inhibit Tregs
	Plant-based ingredient pectin	Butyrate-producing intestinal flora such as *Lachnospiraceae* increases	The gut microbiota metabolite butyrate enhances the expression of DNA binding inhibitory factor 2 in CD8 T cells by inhibiting histone deacetylase, which acts as a key transcription factor for immune cell differentiation and activation, and promotes CD8 T cell proliferation and function through the IL-12 signaling pathway
	Shenling atractylodes soup	The abundance of intestinal bacteria in the genus *Aeroplasma*, *Sutterella*, *Mucispirillum*, *Megamonas* increased, and the structure of intestinal microbiota was optimized	The optimized intestinal microbiota structure promoted the increase of M1 macrophages and the decrease of M2 macrophages and Tregs, and synergized with PD-1 monoclonal antibody to enhance the effect of immunotherapy
	Kudzu root and Qinlian soup	Increased abundance of acid-producing bacteroides, such as *Bacteroides acidifaciens*	*Bacteroides acidifaciens* induces T cell activation and cytokine production through interaction with host intestinal epithelial cells and immune cells to enhance the immune response around the tumor and enhance the host immune response
	Diosgenin	PD-1 monoclonal antibody has a high abundance of probiotics represented by *Lactobacillus genus* that are sensitive to treatment, and a low abundance of *Bacteroides genus* that are not sensitive to treatment	The extracellular polysaccharides secreted by *Lactobacillus* bind to the lysophosphatidic acid receptor of CD8 T cells, induce the expression of CXCR6, promote the infiltration of CD8 T cells into tumor tissues and produce IFN-γ, and enhance the anti-tumor effect of ICIs. The insensitivity of *Bacteroides* to immunotherapy is related to the increased levels of Tregs and MDSCs in the tumor microenvironment

Continued

Regulation strategy section	Targeted regulation of intestinal flora	Improving the mechanism of drug resistance based on the regulation of intestinal microbiota
Plant-based ingredients chestnut tanansulin	The increase in the diversity of intestinal microbiota beneficially changed the composition of intestinal microbiota, and enriched many immune-related intestinal microbiota *Ruminococcaceae*, *Bifidobacterium* and *Alistipes*	Immune-associated intestinal microbiota provides a variety of pathogen-associated molecular patterns that act as ligands for pattern recognition receptors that can be recognized by the host immune system, activate dendritic cells, and induce antitumor T cell responses
Fecal microbiota transplantation	Increased beneficial intestinal flora, such as *Veroncoccaceae*, *Prevotella merdae Immunoactis*, *Ruminococcaceae*, *Bifidobacterium* and *Corynebacterium*, etc.; the abundance of intestinal bacteria that promote immunotherapy tolerance, such as *Bifidobacterium bifidum*, is low	Enhance the activation of CD8 T cells and dendritic cells in the tumor microenvironment, reduce the levels of immunosuppressive cells and immunosuppressive factors, improve the tumor immune microenvironment, and promote anti-tumor response
Probiotics	Eleven kinds of symbiotic bacteria such as *Bacteroides thetaiotaomicron*, *Bacteroides fragilis*, *Bifidobacterium breve*, *Bifidobacterium adolescentis*, *Bifidobacterium longum*, *Lactobacillus reuteri*, *Clostridium difficile*, *Lactobacillus johnsonii*, *Clostridium butyricum*, *Enterococcus faecalis*, *Lactobacillus acidophilus*	Eleven commensal bacteria recruited $GrzB^{+}IFN\gamma^{+}$ CD8 T cells by upregulating the expression of CXCL9, CXCL10 and other IFN-inducible genes in colon epithelial cells, and increased the number of tumor-infiltrating dendritic cells with high expression of MHC class I molecules
	Lactobacillus reuteri	By decomposing dietary tryptophan to produce indole-3-aldehyde, indole-3-aldehyde acts on the aryl hydrocarbon receptor on CD8 T cells, promotes the production of IFN-*γ* by CD8 T cells and enhances the killing of tumor cells, thereby improving the efficacy of ICIs
	Lactobacillus johnsonii and *Clostridium sporogenes*	*Lactobacillus johnsonii* and *Clostridium sporogenes* synergistically produce indole-3-propionic acid, which regulates the stemness program of CD8 T cells by increasing the acetylation of histone H3 lysine 27 in the T cell factor 7 superenhancer region, and promotes their differentiation into T progenitor exhausted CD8 T cells, thereby improving the efficacy of immunotherapy
Prebiotics	Fructan, inulin and lactulose	Increasing the proportion of beneficial bacteria, which helps to improve the effectiveness of immunotherapy by activating and enhancing immune cell function
High-fiber diet	*Ruminococcaceae* enrichment associated with a good immunotherapy response, while *Bacteroidales bacteria* associated with a poor immunotherapy response decreased	A high-fiber diet provides nutrients and promotes the proliferation of beneficial gut bacteria, and fiber is fermented in the intestine to produce short-chain fatty acids that exert anti-tumor effects
Keto diet	Enrichment of specific intestinal flora that produce 3-hydroxybutyrate such as *Akkermansia muciniphila* and *Bifidobacterium adolescentis*	3-Hydroxybutyrate increases the expansion of CD8 T cells induced by ICIs and inhibits the expression of PD-L1, thereby maintaining T cell activation and exerting anti-tumor effects, enhancing the efficacy of ICIs
Vitamin D	Enrichment of the intestinal bacteria genus *Bacteroides fragilis*	Stimulates CD8 T cells to produce IFN-*γ*, enhances the immune response and thus improves the body's immunity to cancer

免疫治疗效果[20,21]。

在肿瘤微环境方面, 由免疫抑制细胞如Tregs、髓源性抑制细胞 (myeloid-derived suppressor cells, MDSCs) 等及其分泌的免疫抑制分子组成的免疫抑制网络是肿瘤免疫逃逸和抗肿瘤治疗耐药的重要原因[22]。黄芪多糖是黄芪的主要成分。黄芪多糖显著地增加免疫治疗内在耐药B16-F10黑色素瘤小鼠中维持肠道稳态和调节免疫反应的*Bifidobacterium pseudolongum*、*Lactobacillus johnsonii*、*Lactobacillus*等肠道菌群丰度, 这些肠道菌群丰度变化与谷氨酸和肌酸等代谢物增加相关。这些代谢物可以抑制肿瘤生长, 减少免疫抑制细胞MDSCs数量并抑制MDSCs相关分子精氨酸酶-1、白细胞介素-10和转化生长因子-*β*的表达, 使肿瘤细胞无法逃避免疫系统的攻击, CD8 T细胞更有效地杀死肿瘤细胞。黄芪多糖具有潜在地改善免疫治疗耐药的作用[23]。

SCFAs是肠道菌群的重要代谢产物, 结合并激活特定的G蛋白偶联受体, 如GPR41、GPR43和GPR109A, 这些受体在免疫细胞上表达, 激活后调节免疫细胞的活性和功能, 提高抗原呈递细胞对肿瘤抗原的识别和呈递能力, 还可以抑制免疫抑制细胞的功能, 这些特性使得SCFAs具有克服免疫治疗耐药的潜力[24]。黄芩苷联合PD-1单抗治疗使PD-1单抗在无应答的Lewis肺癌小鼠中重新发挥抗肿瘤作用, 进一步抑制肿瘤生长。黄芩苷增加了肠道菌群多样性, 其中具有产生SCFAs能力的肠道菌属 *Akkermansia* 和 *Clostridia_UCG-014* 显著增加以及SCFAs含量特别是己酸、丁酸、戊酸表现出明显的增加。有助于提高免疫微环境中的CD8 T细胞水平和诱导CD8 T细胞产生更多肿瘤坏死因子-α (tumor necrosis factor alpha, TNF-α) 和 IFN-γ, 减弱Tregs介导的免疫抑制作用, 从而改善PD-1阻断治疗耐药性[25]。

与健康对照组相比, CRC患者粪便人源化小鼠的PD-1单抗疗效在很大程度上受损。然而, 植物成分果胶显著增强了用CRC患者肠道菌群人源化荷瘤小鼠PD-1单抗的疗效。PD-1单抗加果胶治疗增加了小鼠肿瘤微环境中T细胞浸润和激活, 并且这种有利作用可能是由于肠道菌群代谢物丁酸盐的免疫调节特性。丁酸盐通过抑制组蛋白去乙酰酶, 促进CD8 T细胞中DNA结合抑制因子2 (DNA binding inhibitory factor 2, ID2) 的表达。ID2是免疫细胞分化和活化过程中的关键转录调节因子, ID2可以通过调控IL-12信号通路促进CD8 T细胞的增殖和功能[26]。因此, 果胶依赖于肠道菌群代谢物丁酸盐的免疫调节特性可能有助于改善PD-1单抗治疗耐药性。

肠道菌群通过不同代谢途径影响色氨酸代谢, 产生包含犬尿氨酸等多种代谢产物。犬尿氨酸是一种免疫抑制性代谢产物, 能够抑制抗肿瘤T细胞反应, 帮助肿瘤逃避免疫监视, 防止色氨酸经犬尿氨酸途径代谢, 减少犬尿氨酸积累是改善免疫治疗耐药的关键策略之一[27]。人参多糖和PD-1单抗联合治疗恢复了移植PD-1单抗治疗无反应患者粪便样本的Lewis肺癌小鼠对PD-1单抗敏感性, 人参多糖增加了肠道菌属 *Bacteroides vulgatus* 和 *Parabacteroides distasonis* 丰度以及肠道菌群代谢物戊酸水平, 降低了免疫抑制代谢物 *L*-犬尿氨酸含量、犬尿氨酸/色氨酸比例, 有益于增加外周血、脾脏及肿瘤组织中CD8 T/CD4 T细胞比例以及增强CD8 T细胞分泌IFN-γ、TNF-α和颗粒酶B (granzyme B, GrzB) 的功能, 抑制Tregs作用, 可以有效增强免疫反应, 帮助机体更有效地对抗肿瘤细胞, 减少肿瘤细胞免疫逃逸[9]。

肠道菌群稳态的变化是影响TME的重要因素。肿瘤微环境中M1型巨噬细胞是增强ICIs疗效的重要因子, 而M2型巨噬细胞、MDSCs和Tregs是抑制ICIs疗效的调节因子, 也是导致治疗失败或耐药性的主要因素。保持肠道菌群平衡, 促进肠道有益菌群富集, 增强免疫促进因子作用, 同时抑制免疫抑制因子功能, 改善肿瘤微环境的免疫平衡, 是增强肿瘤患者对ICIs治疗敏感和疗效的重要手段[28,29]。Deng等[30]发现参苓白术汤 (Shenling Baizhu Decoction, SLBZD) 协同替瑞珠单抗 (tirelizumab, TLzmab) 治疗HCT116结直肠癌小鼠能达到更理想、更持久的治疗效果。SLBZD改善ICIs疗效与优化肠道菌群结构相关, 使用TLzmab可以降低实验小鼠肠道菌群的多样性, 而使用SLBZD可以增加肠道菌群的多样性, 表明SLBZD可以修复TLzmab治疗过程中肠道菌群的失衡。SLBZD会增加肠道菌属 *Aeroplasma*、*Sutterella*、*Mucispirillum*、*Megamonas* 的丰度, 优化肠道菌群结构, 从而介导肿瘤免疫微环境中M1型巨噬细胞增加及M2型巨噬细胞和Tregs减少, 与TLzmab发挥协同作用, 提高免疫治疗疗效。

Lv等[31]研究了葛根芩连汤 (GQD) 联合PD-1单抗治疗CT26结直肠癌小鼠的抗肿瘤效果优于PD-1单抗治疗。GQD治疗后肠道中产酸拟杆菌 *Bacteroides acidifaciens* 丰度增加。检测肿瘤组织中免疫浸润情况, 发现PD-1水平较低, IFN-γ、IL-2水平较高, 而低表达PD-1和高表达IL-2是无能T细胞恢复功能的重要指标。*Bacteroides acidifaciens* 作为肠道微生态的一员, 通过与宿主肠道上皮细胞和免疫细胞相互作用, 诱导T细胞活化、聚集和细胞因子产生, 促进肿瘤周围的免疫反应, 从而加强宿主的免疫应答。

Dong等[32]发现, 与其他实验组相比, 薯蓣皂苷元和PD-1单抗联合给药治疗B16-F10黑色素瘤小鼠的效果最佳。对薯蓣皂苷元给药后的小鼠粪便进行微生物分析发现, 对PD-1单抗治疗敏感的以 *Lactobacillus* 为代表的益生菌丰度高, 对治疗不敏感的 *Bacteroides* 丰度低。*Lactobacillus* 能够分泌胞外多糖, 这些胞外多糖通过与CD8 T细胞表面的溶血磷脂酸受体结合, 诱导CXCR6的表达, 促进CD8 T细胞浸润至肿瘤组织并产生IFN-γ, 维持T细胞功能, 从而增强ICIs的抗肿瘤作用[33]。Guardamagna等[34]发现 *Bacteroides* 在肿瘤患者肠道中占主导地位, 与肿瘤微环境中Tregs和MDSCs水平升高有关, 患者对ICIs的反应较差。

特异性免疫原性肠菌在调节ICIs反应中具有重要作用。在晚期黑色素瘤患者中, 瘤胃球菌科基线多样性与肿瘤和外周血中CD8 T细胞比例增加相关, 与良好的免疫治疗反应相关[13]。Meriem等[35]发现PD-1单

抗耐药的E0771乳腺癌肿瘤小鼠中PD-1单抗联合补充植物成分栗木鞣花素可以十分有效地抑制肿瘤生长, 增强PD-1单抗的抗肿瘤活性。栗木鞣花素处理增加了肠道菌群多样性, 有益地改变肠道菌群组成, 富集了许多免疫原菌属*Ruminococcaceae*、*Bifidobacterium*和*Alistipes*。这些肠道菌属可提供多种病原体相关分子模式, 作为模式识别受体 (pattern recognition receptor, PRR) 的配体能够被宿主免疫系统识别并触发免疫反应, 激动各种PRR, 从而激活树突状细胞并诱导抗肿瘤T细胞反应[36]。

2.2 粪便菌群移植逆转肿瘤患者对免疫疗法的耐药性 有研究显示, FMT对荷瘤小鼠免疫治疗有显著影响, 移植了来自对免疫治疗应答者粪便的小鼠对PD-1单抗治疗具有良好的应答, 而使用对免疫治疗无应答患者的粪便进行FMT, 小鼠对PD-1单抗仍然无应答[37]。Baruch教授和Markel教授[38]进行了全球第一项FMT逆转PD-1单抗耐药的临床试验 (NCT03353402), 将接受PD-1单抗治疗后黑色素瘤完全缓解、癌细胞完全消失患者的粪便样本, 经过处理后制作成胶囊, 10名黑色素瘤患者接受胶囊治疗后在3名患者中观察到临床反应, 应答患者肠道中对免疫治疗有利的韦荣氏球菌科、瘤胃球菌科的丰度较高, 可通过诱导Tregs的产生促进免疫治疗耐受的两歧双歧杆菌丰度较低[39]。经过FMT治疗后对PD-1单抗重新应答患者的肿瘤样本中, 有关T细胞活化、主要组织相容性复合物I类 (major histocompatibility complex class I, MHCI) 分子、树突状细胞分化的相关基因水平上调。

研究者发现, 在13名抗PD-1难治性晚期实体癌患者中进行了一项将PD-1单抗与来自抗PD-1反应者的FMT相结合的临床试验。诱导13例患者中有6例发生持续的微生物群变化和临床获益, 其中1例部分缓解, 5例疾病稳定, 客观缓解率为7.7%, 疾病控制率为46.2%。临床反应与血液中细胞毒性T细胞和免疫细胞因子的增加相关。从对FMT有反应的患者中分离出特定细菌, 如*Prevotella merdae Immunoactis*可以刺激T细胞活性并抑制肿瘤生长。FMT结合有益的微生物群可以克服晚期实体瘤对ICIs的抗性[40]。

匹兹堡大学进行的一项临床试验 (NCT03341143)[41]评估了FMT与帕博利珠单抗联合治疗对PD-1单抗耐药黑色素瘤患者的效果。在15名接受联合治疗的患者中, 6名显示临床获益。该联合治疗促进了肠道中瘤胃球菌科、双歧杆菌科和棒状杆菌科的富集, 同时增加了肿瘤微环境中CD8 T细胞的活化, 降低了免疫抑制细胞MDSCs的水平及其IL-8分泌。这表明, FMT可以重塑肠道菌群并改善肿瘤微环境, 从而增强免疫检查点阻断治疗的潜力。

2.3 益生菌、益生元和饮食疗法优化肠道菌群以提高肿瘤免疫治疗反应性 服用益生菌增加肠道有益菌定植, 也是目前靶向肠道菌群调节免疫治疗反应的策略之一。Tanoue等[42]从健康人类的粪便中分离出11种能够刺激CD8 T细胞产生IFN-γ的共生菌株, 与单独给予PD-1单抗治疗相比, PD-1单抗联合11种共生菌治疗后显著抑制肿瘤生长和增强MC38结肠癌小鼠对免疫治疗的反应。其机制是11种共生菌定植上调了结肠上皮细胞中CXCL9和CXCL10以及其他IFN诱导型基因的表达, 从而募集了$GrzB^+IFN\gamma^+$ CD8 T细胞, 增加了高表达MHC I类分子的肿瘤浸润性树突状细胞在结肠中的数量。Bender等[43]研究发现, 口服益生菌*Lactobacillus reuteri*可以定植并持续存在于黑色素瘤中, 通过分解膳食色氨酸产生吲哚-3-醛 (indole-3-aldehyde, I3A), I3A可以作用于CD8 T细胞上的芳香烃受体, 促进CD8 T细胞产生IFN-γ并杀伤肿瘤细胞, 从而增强ICIs的治疗效果。益生菌*Lactobacillus johnsonii*与ICIs治疗效果之间呈正相关。通过补充*Lactobacillus johnsonii*或其产生的色氨酸衍生代谢物吲哚-3-丙酸 (indole-3-propionic acid, IPA) 可以显著增强CD8 T细胞介导的PD-1单抗免疫疗法的效果。在机制上, 以高表达转录因子T细胞因子1 (T cell factor 1, TCF-1由TCF7编码) 为特征的祖细胞枯竭型CD8 T细胞 (T progenitor exhausted CD8 T cells, Tpex) 是PD-1单抗免疫治疗应答的主要亚群。*Lactobacillus johnsonii*与*Clostridium sporogenes*协同产生IPA。IPA通过增加TCF7超增强子区组蛋白H3第27位赖氨酸乙酰化, 调节CD8 T细胞的干性程序, 从而促进CD8 T细胞向Tpex细胞的分化, 提高免疫治疗效果[44]。

益生元是促进肠道益生菌生长并增强其活性的物质, 常见的益生元包括果聚糖、菊粉和乳果糖。益生元有利于益生菌定植和增殖, 抑制病原菌定植, 有抗炎和调节免疫系统的作用[45]。Ramirez-Farias等[46,47]表明, 植物多糖菊粉可升高有益细菌乳酸杆菌和双歧杆菌水平, 而这两个分类群最近被证明对PD-1/PD-L1单抗治疗的应答较好。

饮食和膳食成分对肠道菌群组成的影响被广泛研究[48]。饮食干预5天后肠道菌群开始发生显著变化, 并且是改变肠道菌群组成的一种高效益方式[49]。Spencer等[7]证明, 与低纤维饮食的黑色素瘤患者相比, 高纤维饮食可增加肠道内短链脂肪酸的产生, 使黑色素瘤患者对PD-1单抗治疗的反应更好, *Ruminococcaceae*富集与较好的免疫治疗反应相关, 而*Bacteroidales bacteria*与较差的反应相关。酮饮食可以富集产生3-羟基丁酸

酯的特定肠道菌群 *Akkermansia muciniphila* 和 *Bifidobacterium adolescentis*, 3-羟基丁酸酯可增加ICIs诱导的CD8 T细胞的扩增并抑制PD-L1表达, 进而维持T细胞活化而发挥抗肿瘤作用, 增强ICIs疗效[50]。维生素D通过作用于肠道上皮细胞维生素D受体促进肠道菌属 *Bacteroides fragilis* 的富集, 刺激CD8 T细胞产生IFN-γ, 增强免疫反应从而提高机体对癌症的免疫力, 增强ICIs效果, 抑制肿瘤生长[51]。益生菌、益生元和饮食疗法通过促进肠道菌群的健康平衡, 增强免疫系统抗肿瘤反应。未来的研究需要进一步探索这些干预措施的具体机制和临床应用。

3 靶向肠道菌群改善肿瘤免疫治疗耐药的前景和挑战

靶向肠道菌群调节克服免疫治疗耐药, 提高免疫治疗疗效的策略具有广阔的应用前景, 也存在诸多挑战。

首先, 由于FMT作为治疗手段缺乏长期的安全性研究, FMT的安全性是需要重点关注的问题[52]。受到遗传和环境等多因素影响, 个体的肠道菌群结构存在相当大的差异, 一个健康人的肠道菌群并不一定是肠道菌群失衡患者所需的菌群。更糟糕的是, 目前还无法避免FMT后未知病原体传播的风险。因此, 为解决粪菌移植的安全性问题, 首先, 严格筛选供体, 以确保其健康状态良好并无传染病; 其次, 对移植用的粪便样本进行彻底的病原体检测; 再次, 实施标准化的处理和存储流程, 以减少污染风险; 最后, 持续监测接受者的健康状态, 并建立完善的应急处理机制, 仍然需要继续进行粪菌移植的基础和临床研究, 以深入理解其作用机制, 并优化治疗方案。现有研究虽然普遍认为益生菌似乎对肿瘤患者免疫治疗反应改善有帮助作用, 但也并不是所有的益生菌都有逆转免疫治疗耐药的效果。有研究显示, 用益生菌长双歧杆菌或鼠李糖乳杆菌治疗的小鼠对PD-L1单抗反应较差, 瘤内IFN-γ^+ CD8 T细胞水平降低[53]。同时, 益生菌和受体肠道菌群之间的相容性也是一个需要考虑的问题。益生菌菌株的植入可能会被患者的肠道菌群排斥[54], 也可能会破坏受体肠道菌群的平衡[55]。为应对这些挑战, 首先, 深入研究不同益生菌对免疫治疗的具体作用机制, 以确定其有效性; 其次, 开展更多的临床试验, 以验证哪些益生菌对特定类型的肿瘤和治疗最有效; 最后, 个体化益生菌治疗方案, 依据患者的微生物群特征来选择合适的益生菌。此外, 个体对益生元的反应也存在差异, 有必要基于个体间变异性设计特定益生元配方。另外, 持久采用有益的饮食和生活习惯改变肠道菌群的方式存在不言而喻的困难, 饮食诱导的肠道菌群调节是短暂的。且不同个体的肠道菌群组成存在差异, 同样的饮食可能对不同个体的肠道菌群产生不同的影响。基于个体的肠道菌群组成, 提供个性化的饮食建议, 这可以通过分析个体的肠道菌群类型来定制饮食计划, 以优化健康结果。除了饮食之外, 睡眠、运动和压力管理等生活方式因素也对肠道菌群有影响。建议个体采取全面的生活方式调整, 以支持肠道菌群的健康。最后, 中药复方化学成分复杂, 参与肿瘤免疫治疗耐药的效应和机制方面还需要更多确证性的基础研究和进一步的临床验证。通过药理学和毒理学研究, 筛选出中药复方中对肠道菌群和肿瘤免疫治疗有益的成分, 并优化配方, 去除或降低可能产生干扰的成分; 在中药治疗的同时, 补充益生元和益生菌, 以帮助维持肠道菌群的平衡, 减少耐药性的发生。进行长期跟踪研究, 以监测中药复方对肠道菌群和肿瘤免疫治疗的影响, 以便及时调整治疗方案; 同时, 也需要对中药复方的药效和安全性进行更深入的研究, 以便更好地应用于临床治疗。

由于这些研究的调查队列规模较小, 以及肿瘤病因的复杂性等, 关于特定菌属的作用许多已经发表的文献显示了相互矛盾的结果[53,56,57], 并且关于哪类肠道菌群作为提高免疫治疗反应标志物或者哪类肠道菌群可以降低免疫治疗反应仍然存在不确定性, 可以增加研究的调查队列规模, 提高结果的统计学显著性和可靠性。进行跨多个中心的联合研究, 以减少地域和实验条件的偏差。使用标准化的实验和分析方法, 减少不同研究间的技术和方法差异。在临床研究中验证特定菌属的作用, 结合真实世界数据评估其在不同人群中的效果。另一个突出局限是关于肠道菌群在免疫治疗反应中的作用大多数都是临床前研究发现的, 研究结果存在一定的临床转化限制。使用人源化动物模型来提高临床前研究的相关性和预测能力。运用计算模型和模拟技术预测肠道菌群对免疫治疗反应的影响, 帮助筛选潜在的治疗策略。总之, 肠道菌群作为免疫疗法增效的联合靶点的出现, 为改善肿瘤免疫治疗耐药开辟了新的可能性, 但还需要进一步的研究来建立规范的、作用明确的肠道菌群调节方法。

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