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肠道菌群及其代谢物在白血病及其并发症中作用的研究进展

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【摘要】 白血病是一种源于造血系统的恶性肿瘤,其发病率逐年增加。尽管化疗和造血干细胞移植等传统治疗方法在一定程度上改善了患者的生存率,但仍存在副作用严重、药物耐受及高复发率等问题。近年来,研究发现肠道菌群及其代谢物在白血病的发生、发展及并发症中发挥着重要作用。肠道菌群失衡可导致免疫功能下降和炎症反应加剧,是推动疾病进展的关键因素之一。短链脂肪酸等代谢物通过增强免疫功能和改善肠道屏障修复白血病患者的预后,而硫化氢和胆汁酸等代谢物则在调节肿瘤细胞凋亡和免疫平衡中表现出潜在的抗肿瘤作用。此外,中医药通过调节肠道菌群结构和代谢物显示出缓解白血病化疗副作用的巨大潜力。本文综述了肠道菌群及其代谢物在白血病发生发展及并发症中的作用,并探讨了调节菌群的治疗策略,包括粪便菌群移植、益生菌及中医药干预,进一步为白血病治疗和预后改善提供参考。

【关键词】 肠道菌群;菌群代谢物;白血病;免疫;炎症
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Research progress on the role of the gut microbiota and its metabolites in leukemia and related complication

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【Abstract】 The incidence of leukemia, a malignant cancer originating from the hematopoietic system, is increasing annually. Although traditional treatment method such as chemotherapy and hematopoietic stem cell transplantation have improved patient survival rates to some extent, serious side effects, drug tolerance, and high recurrence rates remain. In recent years, studies have shown that the gut microbiota and its metabolites play an important role in the occurrence, development, and complications of leukemia. Imbalance of the gut microbiota can lead to decreased immune function and an intensified inflammatory response, which is a key factor driving disease

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progression. Some metabolites, such as short-chain fatty acids, enhance immune function and improve patient prognosis through intestinal barrier repair, while others, such as hydrogen sulfide and bile acids, show potential anti-tumor effects exerted through regulation of tumor cell apoptosis and immune balance. Traditional Chinese medicine aimed at regulating the structure of the gut microbiota and its metabolites has shown great potential in alleviating the side effects of chemotherapy for leukemia. This review covers the role of the gut microbiota and its metabolites in the occurrence, development, and complications of leukemia, and explores treatment strategies for regulating the microbiota, including fecal microbiota transplantation, probiotics, and traditional Chinese medicine intervention. We anticipate that this review will serve as a reference for improving the treatment and prognosis of leukemia.

【**Keywords**】 gut microbiota; microbial metabolites; leukemia; immunity; inflammation

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白血病,一种起源于造血系统的恶性肿瘤,涵盖了急性髓系白血病(acute myeloid leukemia, AML)、各种类型的慢性及急性淋巴细胞白血病以及儿童特有的白血病形式[1]。该病的发病人群主要集中在 35~64 岁的中年组,其次是 0~14 岁的儿童组,35~65 岁及以上年龄段的白血病发病率呈逐年上升趋势[2]。其临床表现主要有发热、贫血和肝脾淋巴结肿大等[3]。尽管放射疗法、化学疗法和造血干细胞移植(hematopoietic stem cell transplantation, HSCT)等治疗策略已在一定程度上提升了治疗效果,但治疗过程中的不良反应、耐药、复发等问题依旧是所面临的巨大的挑战[4]。

人体肠道是一个复杂的生态系统,寄居着众多特定的微生物群体。近年来越来越多的研究揭示肠道微生物及其代谢物对白血病的发生、发展和预后中发挥重要的调节作用。肠道菌群及其代谢产物不仅是维持肠道环境稳定不可或缺的因素,而且在维护人体免疫力和抵御病原体方面起着至关重要的作用[5]。研究发现在儿童年龄群中,厚壁菌门的相对丰度减少是易患急性淋巴细胞白血病的危险因素之一[6]。此外调节肠道菌群及其代谢物通过减少炎症和增强免疫可有效减少白血病耐药、复发、感染等问题[7-9]。目前调控肠道菌群治疗白血病已经成为当下的热点话题。因此,本文梳理了肠道菌群及其代谢物在白血病研究的最新进展,为展开进一步研究提供参考。

1 肠道菌群

人体肠道寄居着约 10 万亿个细菌,包括致病菌、共生菌和条件致病菌,共同构成了肠道菌群。微生物群落通过各种生物化学反应与肠道内物质相互作用,维持人体的免疫、代谢和营养等生理功能,对人体健康产生深远影响[5,10]。最新研究发现,与健康儿童相比,白血病患者肠道菌群的组成上存在差异,厚壁菌门的相对丰度上减少,而拟杆菌门的相对丰度增加[6]。白血病化疗后,肠道菌群结构也有明显差异,拟杆菌相对丰度显著降低而其他类群,如梭状芽胞杆菌和链球菌相对丰度增加[11]。进一步研究发现放化疗患者接受益生菌治疗后,胃肠道副作用明显减少,预后改善[12]。且使用如双歧杆菌等有益菌可显著增强嵌合抗原受体 T 细胞免疫疗法(chimeric antigen receptor T-Cell immunotherapy, CAR-T)的疗效,减少 AML 复发[13]。因此,菌群丰富度影响白血病发生、发展,调节菌群丰富度可改善其预后,减少其复发。

2 肠道菌群及其代谢物影响白血病的发生

抑癌基因的突变、免疫功能的缺陷是诱发白血病的关键。研究发现尿石素 B、鞣花酸和没食子酸等肠道菌群代谢物可通过调节肿瘤微环境影响 p53 基因的致癌作用[14]。肠道菌群及其代谢物还可刺激免疫系统,抑制白血病的发生,如 *C. cateniformis* 肠道菌群可下调程序性死亡受体-2 表达来促进抗肿瘤免疫应答[15-17]。另外,研究显示,TET2 基因突变导致的白血病可能与乳酸杆菌等肠道菌群介导的白细胞介素-6(interleukin 6, IL-6)炎症反应有关[18]。菌群代谢物丁酸能够抑制核转录因子(nuclear transcription factor-κB, NF-κB)通路,诱导促炎巨噬细胞死亡,抑制白血

病细胞的生长和增殖[19]。可见,肠道菌群及其代谢物可通过抑制抑癌基因的表达、调节机体免疫和减轻炎症反应,影响白血病发生发展。

3　菌群及其代谢物对白血病预后的影响

3.1　菌群对白血病预后的影响

肠道菌群结构的破坏是白血病预后不良的关键因素之一。肠球菌、脆弱拟杆菌及梭杆菌数量增加会通过介导炎症反应导致白血病感染和移植物抗宿主病(graft versus host disease,GVHD)的发生[20-21]。短链脂肪酸产生菌的缺失通过损害 $CD8^+$T 细胞毒性促进急性淋巴细胞白血病感染的发生[6]。白血病的进一步发展会加重体内肠道菌群的失衡,粪杆菌数量的减少及变形杆菌、肠球菌数量的升高,会导致肠道屏障通透性增加,肠道屏障功能损害,引发内毒素血症等不良反应事件的发生[22]。WANG 等[23]发现普氏栖粪杆菌灌胃可修复 AML 小鼠受损的肠屏障,抑制脂多糖吸收,抑制 AML 进展。可见,菌群结构是白血病预后不良的相关危险因素。

3.2　菌群代谢物对白血病预后的影响

3.2.1　短链脂肪酸

短链脂肪酸是由肠道微生物发酵膳食纤维和非消化性碳水化合物产生的一类有机酸,包括丁酸、乙酸、丙酸,及其丁酸盐、丙酸盐等化合物[24]。WANG 等[23]发现丁酸盐可修复破损的肠道屏障,减少炎症细胞极化而抑制 AML 的进展。CAI 等[25]发现丙酸盐可促进树突状细胞成熟,进一步促进 AML 细胞的有效杀伤。HE 等[26]发现丁酸盐通过激活 IL-12 信号通路,增强细胞毒性 $CD8^+$T 细胞反应来提高化疗药物抗肿瘤疗效。因此,短链脂肪酸可通过调节炎症反应,促进免疫细胞成熟来增强机体免疫,发挥抗肿瘤疗效。

3.2.2　脂多糖

脂多糖是革兰氏阴性肠道细菌细胞壁外膜的主要成分,常在细菌死亡破裂后释放[27]。脂多糖不仅通过激活炎症信号通路促进 AML 发展[28],还可促使 T 细胞增殖、活化等效应功能异常,导致白血病细胞逃避免疫监视[29]。另外,研究发现,维生素 C 通过抑制 ATP 积累和阻碍自噬信号传导,缓解脂多糖诱导的白血病细胞高炎症状态,减少感染的发生[30]。因此,脂多糖一方面通过促进炎症信号,发生炎癌转换,诱导白血病的发生,另一方面通过损害免疫反应,促使了白血病细胞的免疫逃逸。

3.2.3　硫化氢

肠道内多种细菌产生硫化氢,对维持机体内环境稳定和健康至关重要。NGUYEN 等[31]发现硫化氢通过降低抑凋亡基因表达来抑制白血病细胞的恶性增殖,改善白血病的预后。一方面,硫化氢可通过重塑同源半胱氨酸代谢,提升肺癌细胞对铁死亡的敏感性,增强抗肿瘤治疗[32]。ZHANG 等[33]发现一种纳米酶通过释放硫化氢诱导铁死亡,抑制肿瘤。另一方面,研究发现硫化氢气体释放破坏细胞稳态,促进细胞凋亡,还可抑制 ATP 产生,增强对肿瘤的抑制作用[33]。研发现,通过耗尽癌细胞线粒体中的硫化氢,可导致糖酵解显著减少和线粒体损伤,促进肿瘤细胞凋亡[34]。因此,菌群代谢物硫化氢抑制白血病的主要方式可能是调节肿瘤细胞的铁死亡、线粒体凋亡等途径。

3.2.4　胆汁酸

胆汁酸是肝合成并储存于胆囊中的化合物,肠道菌群参与其代谢并产生相关代谢产物[25]。研究发现胆汁酸通过抑制巨噬细胞极化,阻碍 AML 进一步发展[35]。胆汁酸可进一步促进胃肠道调节性 T 细胞(regulatory T cell,Treg)的分化,影响 Treg 细胞和参与炎症反应的 T 辅助细胞 17(T helper cell 17, Th17)之间的平衡[36]。另外,胆汁酸还可降低抗原呈递机制活性和预防肠上皮细胞凋亡,减少 GVHD 的发生和延缓其进展[37]。YIN 等[38]发现使用胆酸盐修饰的纳米颗粒载体能够提高槲皮素的口服生物利用度和治疗指数,抑制白血病发展。可见,胆汁酸可通过减少炎症反应,降低抗原呈递机制活性和预防肠上皮细胞凋亡等抑制白血病进展,减少 GVHD 的发生。

3.2.5　色氨酸

色氨酸代谢途径在白血病的发生进展中扮演着复杂的角色。色氨酸是蛋白质组成和细胞含量最低的氨基酸,肠道色氨酸代谢通路主要包括:吲哚途径、犬尿氨酸途径及血清素途径[39]。有研究发现苯导致儿童白血病的发生可能与色

氨酸代谢物,犬尿氨酸和吲哚-3-丙酸等介质干扰有关[40-41]。而 SHOREY 等[42]发现色氨酸吲哚途径可诱导白血病细胞 G_1 期阻滞和凋亡。含有色氨酸和精氨酸残基的环状细胞穿透肽能有效递送阿霉素,克服耐药性,这为提高化疗药物递送效率和治疗效果提供新策略[43]。可见,色氨酸代谢途径在不同环境下对于白血病的发生和进展表现出双向作用,其深层次机理值得进一步探索。

4 肠道菌群及其代谢物与白血病并发症

4.1 感染

感染是儿童白血病治疗失败的主要原因。而肠道菌群与白血病感染的发生发展关系日益受到关注。STEIN-THOERINGER 等[20]发现肠球菌数量增加,乳酸积累过多,会导致肠黏膜通透性增加,引发内毒素血症。YIN 等[44]发现肠道噬菌体负荷是肠道屏障损伤的一个标志物,与白血病患者单核巨噬细胞激活和全身炎症反应有关。NAKAGAWA 等[45]发现短链脂肪酸通过刺激免疫细胞活性,提高白血病患者的免疫力,抑制感染。广谱抗生素的使用会破坏人体正常菌群,损害机体免疫功能及引发炎症反应,导致感染的发生或进一步加重[46],而 RASHIDI 等[47]发现 FMT 可去除临床相关的抗生素耐药基因肠道定植,减少感染的发生。因此,调控菌群结构对于减少白血病并发感染具有积极作用。

4.2 肠道菌群及其代谢物对出血的影响

出血是白血病常见的并发症,主要表现为皮肤黏膜出血,若出现严重脏器出血,可导致早期死亡发生[48]。BOE 等[49]发现菌群代谢物维生素 K 对几种凝血因子的合成至关重要,可加速血液凝固,减少出血情况发生。JIAN 等[50]发现由菌群及其代谢物介导的肿瘤坏死因子-α(tumor necrosis factor-α,TNF-α)及 IL-6 等炎性介质可导致血管内皮损伤。因此,肠道菌群及其代谢物可通过调控炎性介质来缓解白血病出血。肠道菌群及其代谢物通过促进凝血因子产生及调节炎症细胞因子水平在白血病出血中发挥重要作用。

4.3 肠道菌群及其代谢物对 GVHD 的影响

GVHD 是白血病异体造血细胞移植后,供体淋巴细胞对宿主抗原反应过度引起的一种病理过程,严重可致患者死亡[4]。脆弱拟杆菌及梭杆菌可通过刺激 IL-6、TNF-α、干扰素-γ(interferon-γ,IFN-γ)等炎性介质分泌,促进该并发症的发生发展[21]。吲哚代谢物可通过介导 IFN 反应,减少炎症细胞因子产生,降低 GVHD 死亡率[51]。此外,研究表明短链脂肪酸丁酸盐和丙酸盐可通过促进 Treg 的分化,预防慢性 GVHD 发生及降低 GVHD 风险,提高其生存率[52-53]。BIERNAT 等[8]发现 FMT 增强机体免疫,可降低早期使用广谱抗生素治疗同种异体 HSCT 后感染导致的肠道 GVHD 死亡率及改善类固醇药物抵抗。因此,肠道菌群及其代谢物可通过减少炎症及增强免疫等途径改善 GVHD 不良结局。

5 菌群治疗技术的临床挑战

当前菌群疗法在临床中显示诸多的机遇与挑战。如双歧杆菌等有益菌能够显著增强 CAR-T 细胞免疫疗法的疗效,有效降低 AML 复发的风险[13]。FMT 可通过去除耐药基因及增强机体免疫减少感染发生,降低肠道 GVHD 死亡率[8,47]。乳酸菌通过调节 Th17/T 细胞平衡和限制肠球菌的扩增,明显改善 GVHD 患者预后[54]。有研究进一步表明 FMT 可增强免疫抑制剂的抗肿瘤疗效[55]。然而,FMT 和益生菌的使用并非完全有益,JENQ 等[56]发现乳酸杆菌的丰度超过肠球菌时会刺激 T 细胞重建(包括 TH17),从而促进炎症发展,逆转其治疗作用。BEYER 等[57]发现 FMT 治疗后患者出现空肠梭菌感染,这可能与 FMT 中的某些机会致病菌存在有关。JANS 等[58]发现大肠杆菌菌株可促进基因毒性分子如 colibactin 的传递,引发 DNA 损伤并增加患结肠癌的风险。以上机遇与挑战表明,尽管 FMT 和益生菌在临床治疗白血病中具有潜力,但仍需克服诸多安全性和有效性问题。

6 中医药的调节作用

6.1 调节菌群结构

中医药在治疗血液肿瘤(血症、温病、虚劳、急劳等)疾病已有数千年历史,因其安全性高和低副作用广受青睐。在治疗白血病的过程中,中医药发挥着重要的作用。齐宇镏[59]发现具有温

阳补气作用的参附注射液通过调整肠道菌群结构和保护肠道黏膜屏障,在急性白血病化疗后的阳虚患者中常获得较好疗效。李丹红等[60]发现艾迪注射液通过增加肠道有益菌群数量,扶助机体正气,与化疗合用可显著减轻化疗药物的毒副作用。幽门螺旋杆菌引起肠道菌群紊乱是白血病发生风险因素之一[61],而研究发现清胃和中汤可改善幽门螺旋杆菌引起的肠道菌群紊乱[62]。黄芩贝母汤联合双歧杆菌四联活菌片可通过促进粒细胞和红细胞分化成熟,改善化疗引起的骨髓抑制[63]。因此,中医药调节菌群结构可改善白血病患者的预后,降低不良反应的发生。

6.2 调节菌群代谢物

菌群代谢物是影响白血病进展的重要因素之一。史颖颖等[28]发现中药提取物熊果酸减少肠道内炎症因子的产生,而抑制 AML 的进展。尚广彬等[64]发现肿节风中提取的黄酮类成分可通过上调 L-组氨酸、L-蛋氨酸、黄嘌呤、鞘氨醇、L-精氨酸,下调 1-油酰基甘油磷酸胆碱等代谢物抑制白血病细胞生长。研究显示,精氨酸可促进淋巴和 T 细胞的增殖和活化,增加中枢记忆样 T 细胞的产生,增强巨噬细胞的吞噬和杀伤能力,发挥抗肿瘤作用[65-66]。另外,经典复方如葛根芩连汤[67]、香连丸[68]等被发现具有显著调节菌群代谢物作用。因此中医药调节菌群代谢物抗白血病的研究值得进一步的探索。

7 小结

白血病是一种具有高发病率和复杂病理机制的恶性肿瘤,具有高度异质性,其治疗和预后面临诸多挑战。近年来,肠道菌群及其代谢物在白血病发生、发展及并发症中的重要作用逐渐受到关注。肠道微生物失衡与白血病的发生及预后密切相关,其代谢物如短链脂肪酸、硫化氢和胆汁酸等通过调节免疫功能、炎症反应及肿瘤微环境,对白血病的进展产生显著影响。同时,益生菌如双歧杆菌、乳酸菌、粪便菌群移植和中医药单体及复方在调节肠道菌群和代谢物中展现出良好的治疗潜力,为白血病的干预和治疗提供了新的方向。尽管如此,肠道菌群及其代谢物在白血病中的具体机制仍需深入研究,特别是在个体化治疗和安全性评估方面亟待突破。本研究总结了相关领域的最新进展,为未来更高效的治疗策略提供参考。

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