

肠道菌群对肺癌的影响及中医药调节作用的研究进展

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摘要:从世界范围内来看,肺癌仍然是癌症死亡的重要因素。肠道菌群由于其在肠-肺轴的重要地位,已经成为一个研究肺癌治疗的新热点。肠道菌群可通过基因毒性、免疫反应调节和代谢物质改变等方式影响着肺癌的发生发展。平衡的肠道菌群可以对肺癌的化疗起到增效减毒作用,并且对免疫治疗起到协同作用,积极影响肺癌治疗的疗效及预后,也是肺癌潜在的标志物和靶点。目前益生菌和粪菌移植等通过调节肠道菌群来促进肺癌治疗的方法,尚处在初步探索阶段。中医药与现代医学在肺癌治疗过程中起到协同作用,中医药具有简便廉验的优势,在治疗肺癌的同时可以很好地调节肠道菌群。本文基于肠-肺轴理论就肠道菌群对肺癌的影响,以及中医药在调节肠道菌群中发挥的作用予以综述。

关键词:肠道菌群;肺癌;肠-肺轴;中医药

中图分类号:R273

文献标识码:A

文章编号:1001-6880(2023)Suppl-0175-07

DOI:10.16333/j.1001-6880.2023.S.023

Research progress on the effect of intestinal flora on lung cancer and the regulatory effect of traditional Chinese medicine

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Abstract:Lung cancer is still an important factor in cancer death worldwide. Intestinal microflora has become a new hot spot in the treatment of lung cancer due to its important position in the entero-lung axis. Intestinal microflora can affect the occurrence and development of lung cancer through genotoxicity,immune response regulation and metabolic changes. Balanced intestinal microflora can play a synergistic role in the chemotherapy of lung cancer,and play a synergistic role in immunotherapy,positively affecting the efficacy and prognosis of lung cancer treatment,and is also a potential marker and target of lung cancer. At present,probiotics and fecal bacteria transplantation and other methods to promote the treatment of lung cancer by regulating intestinal flora are still in the preliminary exploration stage. Traditional Chinese medicine and modern medicine play a synergistic role in the treatment of lung cancer. Traditional Chinese medicine has the advantages of simplicity and low cost,and can regulate intestinal flora well while treating lung cancer. This article reviews the relationship between intestinal microflora and lung cancer,and the role of traditional Chinese medicine in regulating intestinal microflora based on the theory of entero-lung axis.

Key words:intestinal microflora;lung cancer;entero-lung axis;traditional Chinese medicine

据 GLOBOCAN 的最新统计数据显示,2020 年世界肺癌发病率为 11.4%,死亡率为 18.0%^[1],肺癌仍是全球最常见的恶性肿瘤。2020 年我国肺癌发病占比 17.9%,死亡占比 23.8%,手术治疗仍然是最主要方式,化放疗、靶向治疗和免疫治疗在治疗过程中起到了主要辅助作用^[2]。随着对肠道菌群

微环境深入研究发现,肺癌的发生发展除了遗传和环境因素外,肠道菌群也起着重要作用,改善肠道菌群或可成为提高肺癌治疗效果的新兴治疗手段^[3]。人体中存在着多种微生物,这些微生物寄生在胃肠道、肺、皮肤和其他器官中,其中胃肠道的微生物密度最高^[4]。微生物群落对于维持宿主微环境的动态稳定方面起着重要作用^[5]。肠肺之间通过复杂的双向淋巴和血液通讯形成肠-肺轴,肠道微生物群

落如果失调,就会通过炎症反应、产生致癌代谢产物等多种途径,改变致癌易感性基因、中断细胞周期以及使免疫检测缺陷,进而促进肺癌发生发展^[6]。恢复稳态的肠道菌群也会通过调节宿主免疫、分泌抗癌代谢产物及协同化疗等方式对肺癌的治疗起到积极意义^[7]。肠道微生物群还可以成为预测肺癌患者免疫治疗敏感性和不良反应的新生物标志物^[8]。目前通过益生菌和粪便菌群移植来调节肺癌患者的肠道菌群的治疗手段尚处在初步探索过程中^[9]。中医药可以增强肺癌化放疗效果、降低药物毒性以及延长患者生存期,近期研究发现中医药在恢复肺癌患者肠道菌群稳态方面也发挥着重要作用^[10]。

1 中医对于肠-肺轴理论治疗肺癌的认识

1.1 中医对肠-肺轴的理解

中医很早就已认识到人体肠肺之间存在着密切关系。《灵枢·本输》记载“肺合大肠,大肠者,传导之脏。”唐孙思邈的《华佗神方》首次提出“肺与大肠相表里”。在《症因脉治·大便秘结论》中秦景明描述:“若元气不足,肺气不能下达,则大肠不得传道之令,而大便亦结矣。”肺宣发肃降、通调水道,大肠传化糟粕,二者以气机升降为功能基础,气血津液为物质基础,在生理上相互影响、相互依存,在病理上肠病及肺、肺病及肠,最终会导致肺肠同病^[11,12]。

1.2 基于肠-肺轴对肺肠疾病的治则治法

中医对肺病及肠病的重要治则是肺肠同治^[13]。《伤寒论·太阳病脉证并治》中记载:“太阳病,桂枝证……喘而汗出,葛根芩连汤主之。”东汉张仲景对伤寒表证未解、邪陷阳明所致的协热下利使用葛根芩连汤肺肠同治。《温病条辨》中论述:“喘促不宁,痰涎壅滞……宣白承气汤主之。”清代吴鞠通对阳明温病出现肺气不降、腑气不通的情况使用宣白承气汤肺肠同治。古代医家可能不知道人体肠道菌群的存在,但在诸多方剂中加入的动物粪便(如夜明砂、望月砂和五灵脂等)或许起到了与现代粪菌移植相似的作用^[14]。

1.3 现代中医基于肺肠同治对肺部疾病的治疗

在肺肠同治的基础上,现代医家对于肺系疾病的治疗既一脉相承又有所创新。Zhou^[15]认为应从整体观念出发对急性呼吸窘迫综合征治疗进行肺肠同治,使用攻下之法使热邪外出,肺气可以随之下降,同时兼顾扶正方可达到祛邪不伤正、补虚不留寇。Xia^[16]认为在对新型冠状病毒肺炎的治疗过程

中,应当采取肺肠同治的治则,在使用宣开之法表里双解的同时,兼顾通腑下利,让膜原疫毒随汗利而出。Wang^[17]在对哮喘病治疗过程中认为,其病因为肺的宣肃失司,大肠传导功能失调,故应肺肠同治,从三焦分消痰饮,用宣肺通腑之法调节气机升降,达到宣肺肃气、化痰通腑、降逆平喘的效果。

2 肠道菌群通过肠-肺轴介导肺癌的现代研究

2.1 肠-肺轴的现代研究机制

现代研究表明,肠肺之间存在一个相互连接免疫系统的双向通信复杂网络,称为肠-肺轴^[18]。膳食纤维在肠道被分解为短链脂肪酸(short-chain fatty acids, SCFAs), SCFAs 可以激活 G 蛋白偶联受体(g-protein-coupled receptors, GPCRs)并抑制组蛋白去乙酰化酶(histone deacetylase, HDAC),促进细胞因子(如 TNF- α 、IL-2、IL-6 和 IL-10)和趋化因子(如 MCP-1 和 cinc2)的产生^[19]。这些细胞产物通过肠黏膜系统进入体循环,通过黏膜相关淋巴组织(mucosa associated lymphoid tissue, MALT),诱导免疫功能应答^[20]。肺部微生物群受到破坏时,会导致肠道菌群受到干扰,肺部免疫细胞与肠道微生物产物之间会相互作用^[21]。肠道菌群紊乱时会通过多种方式影响肺内稳态,从而增加肺部疾病的易感性,肠道菌群平衡时则可以增强肺部对疾病的抵抗力和恢复能力^[22]。环境、饮食、疾病以及医疗干预(如抗生素)等会引起肠道微生物组成和代谢功能的变化,进而影响免疫反应和改变肺部内稳态^[23]。肠-肺轴是一个受肠肺微生物群变化影响及免疫刺激的双向循环系统(见图1)。

2.2 肠道菌群在肠-肺轴中发挥重要作用

肠道菌群是栖息在人体胃肠道内的各种细菌的总称,是一个十分复杂又分布广泛的微生物群落,对于宿主的健康以及肠道正常生理功能有重要意义^[24]。肠道菌群失调会通过多种途径影响肺癌的发生发展。膳食纤维在肠道正常代谢会产生 SCFAs, SCFAs(包括丁酸、丙酸和乙酸等)通过流入身体的外周循环和远端器官,诱导外周免疫细胞分化^[25],随后转运到肺部,调节树突状细胞(dendritic cells, DC)和 T 细胞的活性,调节免疫系统来达到肺内稳态,肠道有益菌群对 SCFAs 的生成有积极意义^[26]。肠道菌群可以通过激活 B 细胞、T 细胞和其他免疫细胞调节肺部免疫反应,其代谢产物也可以调节机体的免疫稳态^[27],如细菌脂多糖可以通过调

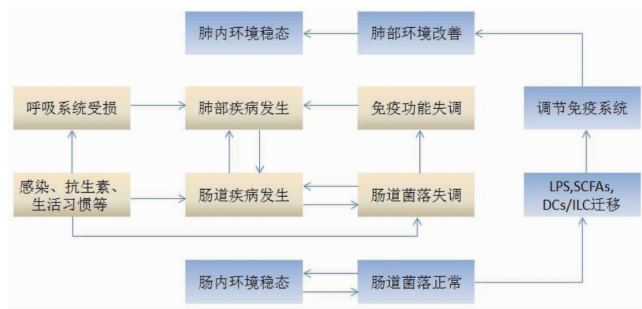


图1 肠-肺轴在肺肠疾病发展过程中发挥调节作用

Fig. 1 Gut-lung axis plays a regulatory role in the development of lung and gut disease

节肺部免疫反应来影响宿主肺部的微生物^[28]。肠道微生物群落通过调节免疫应答、炎症、代谢及基因毒性等途径影响肺部疾病的转归^[29]。

2.3 肺癌患者常见肠道菌群紊乱

肠道菌群发生结构与功能的紊乱状态称为肠道失衡,是肺癌患者常见合并症^[30]。通过对肺癌患者和健康人的粪便基因组分析对比发现,其肠道菌群结构存在显著差异。Liu等^[31]发现肺癌患者的志贺氏菌属、肠杆菌属以及粪杆菌属的丰度较低,拟杆菌属和梭杆菌属数量会有所升高。Zhang等^[32]研究发现肺癌患者志贺氏菌属、大肠杆菌、柔嫩梭菌属和肠杆菌属的水平较低,而拟杆菌属、梭杆菌属和韦荣氏球菌属的丰度会增加。Botticelli等^[33]报道,非小细胞肺癌患者粪便中的普雷沃氏菌属、乳杆菌属、链球菌属、肠杆菌属和拟杆菌属水平显著高于健康对照。肺癌患者肠道菌群特点的不同,提示肠道菌群可能影响肺癌的治疗和预后。

上述研究表明,肺癌患者肠道菌群存在相似的丰度变化,即肠道有益菌群丰度减少且条件致病菌上升^[34],这可能会导致体内循环的SCFAs减少,而SCFAs对肺癌细胞的凋亡及宿主免疫和全身炎症有着重要意义^[35]。

2.4 肠道菌群紊乱促进肺癌发生进展

肠道微生物群结构和功能紊乱会导致肺部免疫稳态的破坏,从而导致肺部疾病易感性增加^[36]。肠道生态失调可以通过基因毒性、系统性炎症和免疫监测缺陷等途径参与肺癌发生进展^[37]。

2.4.1 基因毒性

肠道菌群产生的代谢物具有遗传毒性^[38]。细菌毒素(如细胞致死膨胀毒素(cytolethal distending toxin, CDT)、细胞毒性坏死因子和脆弱拟杆菌毒素等)可以增加精胺氧化酶活性,导致活性氧(reactive

oxygen species, ROS)的产生和双链DNA断裂(DNA double-strand breaks, DSBs),还可以参与细胞增殖与凋亡信号通路,导致相关蛋白表达改变,在宿主体中发挥致癌作用^[39]。

2.4.2 免疫监测缺陷

肠道菌群失调会破坏肺部免疫激活和免疫耐受之间的微妙平衡^[40]。肠道菌群在肠道内激活免疫细胞,这些被激活的免疫细胞随着淋巴液迁移到肺部,参与到肺部免疫反应之中^[41]。过度的免疫反应会导致致瘤性炎症,也会导致免疫监测功能的缺陷,降低机体抗肿瘤能力,从而形成有利于肺癌细胞生长的微环境^[42]。

2.4.3 慢性炎症

肠道细菌不仅影响肺部免疫反应,还可以通过肠-肺轴导致肺部慢性炎症,慢性炎症又与肺癌的发生发展密切相关^[43]。进入肠道黏膜的微生物及其产物激活Toll样受体(Toll-like receptors, TLRs),产生炎症介质和炎症因子,增加外周循环中IL-1 β 水平,将炎症信号传导到肺部激活NF- κ B通路,通过淋巴和血液循环参与肺部炎症过程^[44]。

2.4.4 代谢改变

肠道菌群产生的不同微生物活性分子可以影响宿主的代谢、促进肺癌产生^[45]。去氧胆酸和石胆酸是在肠道菌群作用下产生的二级胆汁酸,它们会导致宿主细胞DNA的损伤,与癌症的发生密切相关。肠道菌群影响机体代谢,会产生乙醛和脱氧胆酸等致癌物^[46]。

2.5 肠道菌群治疗肺癌的生物学机制

由于肠道菌群与肺的密切关系,近年来研究者将注意力转向肠道菌群,希望在肺癌防治方面取得新的突破^[47]。稳态的肠道菌群在调节宿主免疫反应中发挥着关键作用,并通过分泌抗癌产物、对化放

疗增效减毒等方式影响着肺癌的治疗效果^[48]。

2.5.1 调节宿主免疫

肠道菌群通过调节宿主免疫发挥重要抗癌作用^[49]。肠道菌群释放促炎细胞因子信号,促使树突状细胞从癌细胞捕获新抗原以呈现给 T 细胞,激活免疫系统产生对抗癌细胞特异性抗原的效应 T 细胞,被激活的效应 T 细胞入侵肿瘤床,并通过识别特定的肿瘤抗原结合并杀死癌细胞^[50]。

2.5.2 分泌抗癌物质

肠道菌群可以分泌一些活性物质发挥抗癌作用^[51]。肠道有益菌群的代谢产物会影响葡萄糖异构酶 (glucose isomerase, GI) 的活性,抑制致癌因子和癌前病变,也可以减少胆汁酸生成、降低致癌物和诱变物的结合率,以及增加短链脂肪酸含量^[52]。乳杆菌属可以调节 NF- κ B 依赖的基因产物,这些基因产物会进一步调节细胞增殖和生存能力^[53]。

2.5.3 影响化疗疗效

肠道菌群可以对肺癌化疗起到增效减毒的作用^[54]。两歧双歧杆菌通过调节组氨酸代谢,下调肺癌细胞线粒体酪蛋白水解酶 P (caseinolytic protease P, ClpP) 活性,从而提升非小细胞肺癌对铂类化疗药物的敏感性^[55],双歧杆菌属联合化疗,可以减轻化疗毒性,使得肺癌患者的无进展生存期延长^[56]。嗜酸乳杆菌可以增强顺铂的抗肿瘤作用,减小肿瘤体积,提高患者生存率^[57]。

2.5.4 协同免疫治疗

肺癌患者肠道微生物群的多样性与其接受免疫治疗的效果呈现正相关^[58]。肠道菌群能够调节肿瘤对免疫检查点抑制剂 (immune checkpoint inhibitors, ICIs) 的敏感性,如程序性细胞死亡受体 1 (programmed cell death 1, PD-1)、程序性细胞死亡配体 1 (programmed cell death 1 ligand, PD-L1) 和细胞毒性 T 淋巴细胞相关蛋白 4 (cytotoxic T lymphocyte associated antigen 4, CTLA-4)^[59],双歧杆菌属的口服给药通过增强树突状细胞成熟和增加肿瘤微环境 (tumor microenvironment, TME) 中的 CD8⁺ T 细胞数,可以恢复 PD-L1 被阻断的抗肿瘤功效^[60]。

3 中医药对肺癌患者肠道菌群紊乱的临床治疗

肺癌等癌症患者常伴有肠道菌群紊乱引起的里急后重、便溏等消化道反应,中医药在临床治疗中显示出对肠道微生物群稳态良好调节作用^[61]。Pan 等^[62]临床研究表明养阴清肺汤能有效改善肺癌患者放射治疗后皮肤损伤情况,并使得双歧杆菌属、乳

杆菌属等肠道有益菌群的丰度增加,链球菌属等病原菌的丰度降低,调节肠道菌群结构平衡。Xue 等^[63]发现对肺癌患者采取化疗抗癌汤协同治疗后,双歧杆菌属、乳杆菌属等肠道有益菌群的丰度增长显著,同时降低了梭菌属、肠球菌属水平和 IL-6、TNF- α 等炎症因子。Sun 等^[64]研究表明药品祛邪胶囊可以提高 TH 细胞水平,增加肠道抗癌菌和产丁酸菌的丰度,具有抗肿瘤和增强免疫力的双重作用。

4 中药调节肠道菌群的机制

不同中药及药物成分对肠道菌群的调节有所差异。绞股蓝可以维持肠道完整性并恢复大鼠的肠道菌群失调,降低厚壁菌门与拟杆菌门的比例,丰富肠道中的乳球菌属并抑制瘤胃球菌属,还可以使促炎细胞因子 (TNF- α 、IL-1 β 和 IL-6) 和 TLR4 表达下调^[65]。白头翁皂苷可增加大鼠肠道菌群阿克曼氏菌属丰度,降低脱硫弧菌属和瘤胃球菌属丰度,影响大鼠肠道菌群组成与比例^[66]。肉苁蓉多糖能调节肠道菌群多样性,增加有益菌群,特别是能促进普雷沃氏菌属的生长,提高短链脂肪酸的产生和棘皮苷的吸收^[67]。小檗碱合 6-姜烯酚治疗小鼠后,其肠道菌群 Simpson 等指数显著升高,芽孢杆菌属逐渐增多,疣微菌门显著减少,阿克曼氏菌属基本完全消失,改善菌群结构,促进肠道微生态平衡^[68]。茯苓多糖可以显著增加粪杆菌属的相对丰度,并降低肠道细菌来源的内毒素负荷水平,重塑肠道细菌的组成,还可以下调与免疫和炎症相关的通路的表达^[69]。

葛根苓连汤治疗可恢复肠道菌群稳态,导致阿克曼氏菌属、脱硫弧菌属和乳杆菌属增加,大肠杆菌减少,通过肠道菌群影响全身免疫^[70]。健脾固肠方能够增加肠道微生物群多样性,增加肠道益生菌群丰度,调节 Th17/Treg 细胞平衡,调节免疫系统,对肺癌细胞的侵袭和转移起到了抑制作用^[71]。益气养阴方联合顺铂治疗后,小鼠血清 IL-6、IL-10 及 TNF- α 含量降低,厚壁菌门、乳杆菌属明显升高,拟杆菌门比例显著减低^[72]。补肺消积饮可以通过减少 IL-1 β 和 IL-18 的产生,抑制 NLRP3 炎症小体活化从而抑制肿瘤生长,治疗后肠道内疣微菌门、厚壁菌门的丰度得到增加,并降低拟杆菌门、变形菌门数量,补肺消积饮可以平衡肺癌肠道微生物组成^[73]。半夏泻心汤减少肠杆菌属和肠球菌属丰度,促进双歧杆菌属和乳杆菌属的生长;肠道菌群对生物碱类成分主要进行脱甲基、脱甲氧基、脱亚甲二氧基、加

氢还原及氧化作用,对黄酮类成分主要进行脱糖及甲基化作用^[74]。

5 总结

随着肠-肺轴的进一步研究发现,肠道菌群失调是肺癌发生发展的重要因素,肠道菌群通过基因毒性、调节免疫反应和代谢产物等促进肺癌发生发展^[75]。恢复稳态的肠道菌群也可通过调节机体免疫系统、分泌抗癌物质、协同化疗和免疫治疗的途径,在肺癌治疗过程中起到积极作用,未来可能成为预测肺癌治疗效果的新靶点^[76]。目前益生菌和粪菌移植等调节肠道菌群平衡治疗肺癌的方法仍处于探索阶段^[77]。中医药对肠道菌群的恢复有积极作用,可以显著改善菌群结构,调节肠道微生态平衡,且具有简便廉验的优势,对通过调节肠道菌群治疗肺癌有重要的意义。目前对于中医药调节肠道菌群的研究主要停留在检测粪便菌群基因组以探究菌群构成,对于靶向影响到哪些肠道菌群的信号通路还没有深入的研究,而这对肺癌的精准治疗有重要意义,中医药调节肠道菌群治疗肺癌的进一步研究还需要国内外学者的继续努力。

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