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中药现代化

·专题报道·

“肺与大肠相表里”的黏膜免疫调节机制及中药干预作用研究进展

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[摘 要] “肺与大肠相表里”是中医学经典理论之一,揭示了肺与大肠在生理、病理上的密切相关性,在肺、肠疾病治疗上具有重要指导意义。现代医学已揭示肺与大肠在组织来源、黏膜免疫上的联系,初步明确了“肺与大肠相表里”的物质基础及可能的调节机制,并将此理论应用于2019冠状病毒病、溃疡性结肠炎等肺肠难治病的治疗,获得可靠疗效。现有研究结果表明,肺与大肠解剖上的同质性促使了肺-肠黏膜免疫功能的相关性,黏膜免疫及固有淋巴细胞的迁移归巢是肺与大肠共享生理病理的调节机制之一。部分清热解毒类中药和补益类中药通过调节肺-肠黏膜免疫功能治疗肺、肠疾病,成为“肺肠同治”创新药物研发的候选药物。然而,上述两类中药现有免疫调节相关研究主要集中于对分泌型IgA、细胞因子等表达水平及固有淋巴细胞、B淋巴细胞等免疫细胞数量的变化上,对与之相关的气道、肠道黏液高分泌、肺及肠道黏膜屏障免疫细胞功能改变、肺-肠黏膜免疫相互作用动态过程及肺-肠局部微生态的干预作用,以及清热解毒、补益功效与其调节肺-肠黏膜免疫作用间的相关性和生物学基础等尚缺乏深入研究。本文试从肺、肠共同拥有的黏膜免疫系统切入,从黏膜固有淋巴细胞归巢角度分析肺肠相关疾病的内在联系,并综述对肺、肠黏膜免疫具有调节作用的中药复方及其有效成分的作用特点和规律,为“肺与大肠相表里”理论内涵的深入阐释及相关疾病治疗药物的研发提供参考。

[关键词] 肺-肠轴; 免疫,黏膜; 固有淋巴细胞; 淋巴细胞归巢; 中医药治疗
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Mechanism and intervention of mucosal immune regulation based on “lung and large intestine being interior-exteriorly related” theory of traditional Chinese medicine

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[**Abstract**] The "lung and large intestine being interior-exteriorly related" is one of the classical theories in traditional Chinese medicine, which indicates a close correlation between the lung and large intestine in physiology and pathology, and plays a pivotal role in guiding the treatment of the lung and bowel diseases. Modern medicine has revealed some connections between the lung and large intestine in tissue origin and mucosal immunity, and preliminarily illuminated the material basis and possible regulatory mechanism of the theory. Recently, this theory has been applied to guide the treatment of refractory lung and intestine diseases such as COVID-19 and ulcerative colitis and has obtained reliable efficacy. Existing research results show that the anatomical homogeneity of lung and large intestine promotes the correlation between lung-bowel mucosal immunity, and mucosal immunity and migration and homing of innate lymphocytes are one of the physiological and pathological mechanisms for lung and large intestine to share. Under the guidance of this theory, Chinese medicines with heat-clearing and detoxifying or tonic effects are commonly used in the treatment of the lung and intestinal diseases by regulating lung-bowel mucosal immunity and they can be candidate drugs to treat lung/intestinal diseases simultaneously. However, the existing studies on immune regulation are mainly focused on the expression levels of sIgA and cytokines, as well as the changes in the number of immune cells such as innate lymphocytes and B lymphocytes. While the following aspects need further investigation: the airway/intestinal mucous hypersecretion, the functional changes of pulmonary and intestinal mucosal barrier immune cells, the dynamic process of lung/intestinal mucosal immune interaction, the intervention effect of local pulmonary/intestinal microecology, the correlation and biological basis between the heat-clearing and detoxifying effect and the tonic effect, and its regulation of pulmonary/intestinal mucosal immunity. In this paper, we try to analyze the internal relationship between lung and intestine related diseases from the point of view of the common mucosal immune system of lung and intestine, and summarize the characteristics and rules of traditional Chinese medicine compound and its active ingredients, which have regulatory effect on lung and intestine mucosal immune system, so as to further explain the theoretical connotation of "lung and large intestine being interior-exteriorly related" and provide reference for the research and development of drugs for related diseases.

[**Key words**] Lung-gut axis; Immunity, mucosal; Innate lymphocytes; Lymphocyte homing; Traditional Chinese medicine treatment

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"肺与大肠相表里"理论是中医藏象学说的重要内容,是中医对"肺"与"大肠"在解剖位置、经络循行、生理病理之间辩证统一关系的高度概括,是中医整体观的体现。肺与大肠的关系首见于《灵枢·本输》:"肺合大肠,大肠者,传导之腑";《灵枢·经脉》记载了手太阴肺经和手阳明大肠经的络属关系。两者在生理上相互依存,在气机宣降和津液输布功能中相互协调、相互制约,共同维持机体健康;肺气的肃降有助于大肠传导功能的发挥,而大肠的传导功能正常,又有助于肺气的肃降[1]。病理上肺与大肠相互影响、相互传变,肺之肃降生理功能的改变会对

大肠腑的顺降气机产生明显的影响,介导由肺及肠的病理改变;而大肠传导功能发生异常可引发咳嗽、气喘等肺失宣肃的症状[2]。研究证明,50%成年炎症性肠病患者存在肺炎或肺功能受损现象[3-5],肠病可影响肺中降钙素基因相关肽、P物质、血管活性肠肽等的表达[6],肺内气道高敏反应可导致肠道炎症发生[7-8]。治疗上两者相互为用,肠病治肺而愈,肺病治肠而愈[9-14]。近年来,越来越多的证据验证了“肺与大肠相表里”现象客观存在及其科学性[15-17],应用该理论指导2019冠状病毒病[18-19]、溃疡性结肠炎[20]等难治病的治疗疗效受到研究者们关注。本文试从肺、肠共同拥有的黏膜免疫系统切入,从黏膜固有淋巴细胞归巢角度分析肺肠相关疾病的内在联系,希望该理论在肺、肠疾病治疗中发挥更好的指导作用;同时从文献中筛选对肺、肠黏膜免疫具有调节作用的中药复方及其有效成分,分析其作用特点和规律,为“肺与大肠相表里”理论内涵的深入阐释及相关疾病治疗药物的研发提供参考。

1 “肺与大肠相表里”的生物学基础

从胚胎发育的角度,肺、气管由肠的前肠发展而来,呼吸道上皮和膜体由原肠内胚层分化而成,肺和结肠、回肠在胚胎组织的发生上具有同源性[21-22]。肺和肠道是直接与外界接触的器官,两者均具有典型的、由上皮和固有层组成的黏膜结构,同属公共黏膜免疫系统。肺、肠黏膜均能分泌的分泌型免疫球蛋白A(sIgA)是体现“肺与大肠相表里”的重要分子生物学基础[23]。菌群可能是联系肺-肠的物质基础之一[24]。肠道微生物群可影响远端肺部的免疫应答[25],肠道微生物种类和代谢产物的改变与肠/肺免疫异常、炎症发生以及过敏、哮喘、慢性阻塞性肺疾病、急性呼吸窘迫综合征和肺癌等肺部疾病的发展有关[26-27]。在呼吸道流感病毒感染的小鼠模型中,招募到小肠的肺源$CCR9^+CD4^+$ T细胞产生的γ干扰素通过调节肠道菌群的组成,介导肠道疾病的发生[28];肺树突状细胞能够诱导高水平的肠道归巢整合素,使T细胞迁移到肠道,介导肠道保护性免疫[29]。综上可知,肺与大肠解剖上的同质性促使了肺-肠黏膜免疫间的相关性,肠道和肺之间存在密集的免疫对话,肺-肠轴是由肠道和肺部微生物及其局部和长期免疫相互作用所形成的一种特殊联系,黏膜免疫是肺与大肠共享生理病理的基础之一。

2 肺与大肠共享生理病理的主要免疫调节机制

黏膜免疫是连接肺和肠道的桥梁,肺-肠可分别作为诱导部位和效应部位,通过黏膜淋巴细胞归巢建立共同黏膜防御机制[23]。固有淋巴细胞(innate lymphoid cells, ILC)是一种具有获得性免疫功能的免疫细胞,其在调节免疫防御、组织修复、代谢平衡和炎症反应中具有重要作用。ILC根据分泌细胞因子的不同,分为分泌γ干扰素的ILC1,分泌IL-5、IL-9、IL-13的ILC2以及分泌IL-17、IL-22的ILC3[30]。其中,ILC2和ILC3尤其是ILC3与“肺与大肠相表里”关系密切[31-32]。

ILC2主要位于肠道和呼吸道黏膜组织。肠道中,ILC2响应上皮细胞分泌的细胞因子IL-25,协同Th2细胞产生IL-5、IL-9等细胞因子,并招募嗜酸/嗜碱性粒细胞、肥大细胞及产生IgE的B细胞,促进肠道炎症的产生[7]。肠道中的ILC2可通过肠系膜淋巴系统进入血液循环,从肠道迁移至肺部,参与肺部的免疫炎症反应[33]。肺内气道高敏反应呈ILC2依赖性,ILC2产生的IL-13通过促进肺部激活的树突状细胞进入引流淋巴结,使幼稚T细胞向Th2分化,产生获得性Th2细胞免疫[8]。

ILC3包括产生IL-22的ILC3[34](又称ILC22、NK22、NKR-LTi、NCR22[35]),产生IL-17A和γ干扰素的NCR^- IL-$17A^+$ IFN-γ^+ ILC3[36]以及NCR^- IL-$17A^+$ ILC3[37]。ILC3主要分布于肺、肠黏膜屏障,通过分泌细胞因子与适应性免疫系统相互作用,在机体免疫和黏膜屏障稳态调节中起重要作用[38-40]。ILC3是人类肺组织中最常见的淋巴细胞类群,在慢性阻塞性肺疾病患者中表达明显增加[41];ILC3及其分泌的IL-17、IL-22和巨噬细胞集落刺激因子参与病毒感染、细菌性肺炎及慢性阻塞性肺疾病等肺部疾病的免疫调节[42]、上皮细胞稳态的维持以及炎性损伤后上皮细胞的修复和再生[39]。在肺炎克雷伯菌介导的肺部感染中,被招募到肺部的趋化因子C-C-基元受体2(CCR2)阳性炎性单核细胞分泌TNF-α,通过上调肺上皮细胞表达趋化因子CC趋化因子配体20(CCL20),促进分布在肠道的ILC3募集到肺感染

部位并分泌 IL-17A,增强单核细胞介导的细菌摄取和杀伤作用[43]。在肠道,ILC3 分泌的 IL-22 和信号传导和激活因子 3(STAT3)对控制急性肠黏膜细菌感染、维持肠道免疫至关重要,视黄酸受体相关孤儿受体 γt(RORγt)阳性 ILC3 的功能及 IL-22的转录受 STAT3 信号通路调节[44];RORγt 阳性 ILC3 是肠道中巨噬细胞集落刺激因子(Csf2)的主要来源,肠道共生菌驱动的边缘中性粒细胞池(MNP)-ILC-Csf2 轴是肠道内免疫稳态的关键调节因子[45]。值得注意的是,由 ILC3 异常分泌的 IL-17 可导致哮喘、肺炎以及肺纤维化等呼吸道病理改变[46],介导气道高反应性[38]及持续的肠道炎症反应[47-49]。

除 ILC 介导的黏膜免疫调节机制外,肺肠之间还存在微生物介导的免疫调节作用[50]。肠系膜淋巴系统是肺和肠之间的重要通道,完整的细菌及其片段或代谢物(如短链脂肪酸)可通过它跨肠屏障移位,进入体循环,调节肺的免疫应答[51-53]。幽门螺杆菌提取物通过诱导 Batf3 依赖的肠道 $CD103^+$ $CD11b^-$ 树突状细胞在肺部富集及分泌 IL-10 可改善过敏性哮喘症状[54-55];粪菌移植在有效治疗肺炎继发抗生素相关性腹泻的同时,对肺炎也有缓解作用[56]。由上述可知,以 ILC3、ILC2 为代表的 ILC 及肺、肠微生物是“肺与大肠相表里”共享生理病理的黏膜免疫关键调节因子和潜在作用靶点。

3 肺与大肠病理传变的固有淋巴细胞迁移归巢调节机制

黏膜淋巴细胞归巢是黏膜免疫的重要活动之一。黏膜淋巴细胞表面的归巢受体与位于黏膜部位血管内皮细胞上的黏膜地址素之间的特异识别,是黏膜淋巴细胞定向迁移以及肺、肠黏膜组织间建立共同黏膜免疫防御或病理传变的生物学基础[7,32,48]。研究表明,肠 ILC3 高表达趋化因子受体(CCR)9,肠系膜淋巴结 T-bet 阴性 ILC3 和 T-bet阳性 ILC3 中高表达 CCR7,$CCR7^{-/-}$ 小鼠肠系膜淋巴结、$CCR9^{-/-}$ 小鼠小肠及 $Itg7\beta^{-/-}$ 小鼠结肠中 ILC3 分布数量下降;黏膜树突状细胞分泌的视黄酸能诱导肠归巢受体 CCR9 和 α4β7 表达,促使 $CD90^+$ $CD127^+$ ILC 中 $CCR7^+$ $CCR9^-$ $\alpha4\beta7^-$ 向 $CCR7^-$ $CCR9^+$/$\alpha4\beta7^-$ 转变,诱导外周血中的 ILC3 向小肠和结肠迁移;ILC3 及其归巢受体能有效恢复维生素 A 缺乏宿主的黏膜免疫缺陷[57]。肠壁 $CX3CR1^+$ 髓细胞通过表达 CXCL16 与 $CXCR6^+$ $NKp46^+$ ILC3 相互作用,促进 ILC3 在肠道的聚集及分泌 IL-23 的树突状细胞诱导活化[58]。结肠炎中,ILC3 分泌的巨噬细胞集落刺激因子招募髓系炎性单核细胞在肠道聚集介导了结肠炎的进展,阻断巨噬细胞集落刺激因子可抑制 ILC3 从肠道固有层隐窝斑中的动员及活化[59]。此外,非特异性归巢受体也可促使淋巴细胞介导结肠炎中肺、肠的病理改变。在炎症性肠病活动性炎症期间,表达非组织特异性趋化因子受体 CXCR3、CCR5 和 CCR2 的 ILC 在肠道黏膜富集,这些细胞通过系统内循环,错误归巢到肺组织,促进了炎症性肠病的淋巴细胞性肺泡炎[60-61];而 $CCR7^+$ 记忆 T 细胞的错误归巢可有效激活归巢部位的树突状细胞,并在再次刺激后向 $CCR7^-$ 效应细胞分化,介导炎症产生[62]。

肺和肠道树突状细胞介导了 ILC 在肠道-肺黏膜免疫系统间的迁移和归巢[29,57]。在新生期特定发育窗口内的肠道共生菌暴露对小鼠肺黏膜免疫发育具有重要意义。新生小鼠肠道 $CD103^+$ $CD11b^+$ 树突状细胞从共生菌中捕获抗原,诱导肺归巢信号 CCR4 在 $IL\text{-}22^+$ ILC3 上表达,促进 $IL\text{-}22^+$ ILC3向肺部转运及积累,促进肺 IL-22 依赖的黏膜防御,增强新生小鼠对肺炎的抵抗力;共生细菌破坏可导致新生小鼠肺中产生 IL-22 的免疫细胞功能发生持久变化,从而增加对肺炎的易感性[25]。荚膜组织胞浆菌感染小鼠给予 TNF-α 拮抗剂可诱导肠道独有的 $CD11b^+$ $CD103^+$ 树突状细胞通过干扰素调节因子 4(IRF4)和 Notch2 依赖的途径从肠道经血液迁移到肺,并通过分泌视黄酸诱导外周调节性 T 细胞向肺部聚集,增加小鼠对荚膜组织胞浆菌的易感性;阻止 $CD11b^+$ $CD103^+$ 树突状细胞从肠道到肺部的迁移或能防止中和 TNF-α 介导的细菌易感性[63]。炎症性肠病患者肠道炎症黏膜 $CD103^+$ 树突状细胞数量减少与其迁移有关,给予 TNF-α 拮抗剂阿达木单抗能有效逆转此现象[64-65]。可见,调节肺、肠炎症性疾病中肺、肠黏膜 ILC 迁移归巢,能有效改善“肺”与“大肠”间的病理传变,阻断肺病及肠或肠病及肺过程。

4 基于“肺与大肠相表里”的中医药实践及其黏膜免疫调节作用

4.1 基于“肺与大肠相表里”的临床实践及现代研究

临床研究显示,宣肺通便方治疗功能性便秘疗效显著[14];采用粪菌移植技术治疗肺炎继发抗生素相关性腹泻能有效改善肺部炎症及结肠溃疡,减轻腹痛、腹泻症状[56];治疗溃疡性结肠炎时佐以补肺中药,可提高治愈率,降低复发率[66];泻下中药复方——大承气汤可改善急性呼吸窘迫综合征患者的氧合指数和肺水肿,降低机械通气的并发症和患者病死率[13];通腑解毒汤辅助西药治疗小儿重症肺炎可提高疗效、缩短病程[67];泻肺通腑方药能降低老年重症肺炎合并胃肠功能障碍患者的肺部感染评分,缩短抗生素暴露、机械通气时间,提高综合疗效[68]。苏子降气汤合宣白承气汤及宣降汤可分别用于治疗慢性阻塞性肺疾病及慢性支气管炎合并功能性便秘者[69]。

现代药理研究表明,“肺肠同治”代表方剂宣白承气汤能有效降低脂多糖诱导的急性肺损伤大鼠肺组织 P 物质水平,改善肺水肿及肺组织病理学改变[9];能降低脂多糖加熏香烟诱导的慢性阻塞性肺疾病模型大鼠外周血及肺泡灌洗液中细胞因子水平,改善肺部炎症反应[17]。灌胃给予容积性泻下药芒硝能有效降低卵清蛋白诱导的过敏性哮喘小鼠气道阻力及肺泡灌洗液中嗜酸性粒细胞、淋巴细胞总数及血清 IgE 含量,抑制气道炎症[70]。肠道疾病治疗方药葛根芩连汤能有效改善脂多糖诱导的急性肺损伤小鼠肺水肿及微血管渗透性,下调 TNF-α、IL-1β 和 IL-6 水平,抑制肺部炎症反应及肺上皮细胞和内皮细胞凋亡[71];大承气汤能降低哮喘及肺肠合并模型大鼠外周血淋巴细胞中 Th17 淋巴细胞比例及血清 IL-6、IL-17 水平,调节 Th17 与调节性 T 细胞的平衡,减少哮喘发生[10];健脾固肠方通过减少肺癌小鼠肠道淋巴组织调节性 T 细胞、Th17 细胞相关叉头框蛋白 P3(FoxP3)、RORγt 转录因子的表达,调节肠道免疫平衡,抑制肺癌侵袭转移[12]。黄芪桔梗汤从肺论治能有效降低 2,4,6 一三硝基苯磺酸(TNBS)-乙醇诱导的溃疡性结肠炎大鼠肺与结肠组织黏膜中 sIgA 和 IL-4 水平,减轻肺和结肠组织病理损伤[11];鱼腥草多糖能抑制甲型 H1N1 流感病毒小鼠肺组织 TLR4 和 NF-κB 蛋白表达及 TNF-α、IL-6、IFN-α 等细胞因子分泌,改善肺组织损伤,增加肠道 sIgA 分泌及肠黏液中 IgA 水平,上调肠上皮紧密连接蛋白闭锁小带蛋白 1(ZO-1)表达,保护肠道机械及黏膜屏障,实现肺肠同治[72]。上述研究表明,中药复方及其活性成分可通过调节肺、肠相关免疫反应,抑制炎症反应、改善黏膜屏障损伤等,阻断肺-肠间的病理传变,实现肺病治肠而愈和肠病治肺而愈。

4.2 中药复方及其活性成分对肺、肠黏膜的免疫调节作用

4.2.1 对生理状态肠黏膜免疫的调节作用 中药复方及其多糖部位对正常机体具有适度的免疫调节作用。加味四君子汤能升高健康仔猪血清 IFN-γ、IL-2、IL-4、IL-6 水平,促进肠黏膜上皮及固有层 sIgA 蛋白和 mRNA 表达水平及 sIgA 分泌,增强仔猪机体免疫机能[73]。中药四黄提取物、黄芪多糖能增加家禽肠道黏膜淋巴细胞及 IgA^+ 细胞数量,促进 IgA 分泌,提高肠道免疫功能[74-75];板蓝根多糖、枸杞多糖、玉屏风散多糖可通过增加小鼠小肠黏膜上皮内淋巴细胞、杯状细胞、肥大细胞及 IgG^+、$sIgA^+$ 细胞数量,增加外周血 $CD3^+$、$CD4^+$、$CD8^+$ T 淋巴细胞数量,促进 IL-2、sIgA 的分泌,增强免疫作用[76-78];人参多糖和猪苓多糖在体外能活化肠黏膜派氏集合淋巴结中 T 淋巴细胞,诱导 γ 干扰素生成,发挥免疫促进活性[79]。

4.2.2 对环磷酰胺致免疫功能低下状态肺、肠黏膜免疫的调节作用 补益类中药及其多糖成分能改善环磷酰胺诱导的肺、肠黏膜免疫功能低下。玉屏风散能增强环磷酰胺致免疫功能低下小鼠腹腔巨噬细胞吞噬功能、溶血素抗体生成,促进呼吸道和消化道 IgA 分泌;玉屏风散多糖能增加免疫功能低下小鼠肠黏膜派氏集合淋巴结数量及 IgA^+、$CD3^+$ 细胞数,激活肠道黏膜免疫,提高肠道 IgA 分泌水平[80],并能促进淋巴细胞向肺、肠黏膜归巢,增强 NK 细胞活性,改善环磷酰胺介导的免疫损伤[81]。黄芪多糖[82]、太子参多糖[83]、“芪苓”制剂多糖[84]能改善环磷酰胺致免疫功能低下小鼠肠道菌群结构,增加小肠黏膜派氏集合淋巴结面积及肺、肠道上皮淋巴细胞和杯状细胞数,促进 sIgA、IL-2、IL-6、γ 干扰素分泌,改善环磷酰胺诱导的肠道黏膜损伤。

4.2.3 对病理状态肺、肠黏膜免疫的调节作用

由清热解毒类中药组成的中药复方和活性成分对各类致病因素介导的肺、肠黏膜局部免疫功能异常具有良好的调节作用。在肺黏膜免疫调节方面,中药退热方(石膏 20 g,知母、黄芩、玄参、柴胡、栀子各 10 g,射干、桔梗各 5 g)能提高甲型流感患儿 sIgA 与白蛋白比值,增强呼吸道黏膜免疫功能,其退热时间短于应用奥司他韦的患儿[85-86];解表方麻黄汤(麻黄 9 g,桂枝、杏仁各 6 g,甘草 3 g)、银翘散(连翘、金银花各30 g,苦桔梗、薄荷、牛蒡子各 18 g,生甘草、淡豆豉各 15 g,竹叶、芥穗各 12 g)能提高寒冷刺激诱导的上呼吸道黏膜免疫功能低下模型小鼠唾液 sIgA 含量及溶菌酶活性,降低链球菌肺炎小鼠死亡率,延长生存时间[87];银莱汤(金银花、莱菔子、黄芩、连翘、鱼腥草、前胡、瓜蒌)能增强食积复合 FM1 流感病毒感染小鼠肠黏膜局部免疫功能,促进 sIgA 分泌,适度调节 TNF-α、IL-10等细胞因子水平,改善肠黏膜屏障损伤,防治食积呼吸道感染疾病[88]。疏风解毒胶囊能降低肺炎链球菌致肺炎大鼠外周血 B 淋巴细胞、$CD8^+$比例和 IL-1β、TNF-α、IFN-α 等细胞因子及 IgM 等免疫球蛋白水平,升高外周血 $CD4^+/CD8^+$及 NK 细胞比例,抑制过度免疫介导的肺部炎症反应[89]。人参皂苷 Rg1 能减少肺组织中性粒细胞及 M2 型巨噬细胞浸润,抑制 NF-κB 磷酸化,保护脂多糖诱导的急性肺损伤[90]。

在肠黏膜免疫调节方面,七味白术散可增加肠黏膜 sIgA 表达,改善肠黏膜炎性病变,对抗抗菌药物联合番泻叶致菌群失调小鼠肠黏膜损伤[91]。藿香正气液能上调结肠灌注乙酸致感染后肠应激综合征大鼠血清 IL-10 水平,促进 sIgA 分泌,抑制结肠黏膜组织 NF-κB p65、p38 MAPK、细胞间黏附分子 1 表达,上调结肠黏膜 ZO-1 等表达,改善结肠上皮细胞超微结构,保护肠黏膜屏障损伤[92];藿香正气双向胶囊能增加福氏痢疾杆菌和鼠伤寒沙门菌所致腹泻小鼠外周血及肠道黏膜派氏集合淋巴结 $CD8^+$ T 淋巴细胞数,降低 $CD4^+/CD8^+$比例及 TNF-α 水平,改善腹泻症状[93];通腑颗粒能增加尾静脉注射脂多糖致内毒素血症大鼠肠黏膜树突状细胞和 $CD4^+$、$CD8^+$T 细胞及 IgA^+B 细胞数量,调节 Th1/Th2 细胞比例,减少淋巴细胞凋亡,改善肠黏膜免疫损伤[94]。大豆异黄酮[95],人参皂苷 Rb3、Rd[96]能增加肥胖大鼠及 $Apc^{min/+}$小鼠小肠黏膜上皮内淋巴细胞和杯状细胞的数量,改善肠黏膜免疫屏障结构;巴豆霜-大黄多糖药对能改善溃疡性结肠炎大鼠 T 淋巴细胞亚群比例,降低黏膜地址素细胞黏附分子(MadCAM-1)和细胞间黏附分子 1 的表达,减少 $CD8^+$T 淋巴细胞过度归巢,改善肠黏膜免疫功能亢进,改善肠道炎症反应[97];小檗碱可降低糖尿病大鼠肠道肠系膜淋巴结中调节性 T 细胞及 $CD11b^+$ $CD68^+$细胞比例,抑制 IL-1β 和 TNF-α mRNA 表达,上调 IL-4 和 IL-10 mRNA 水平[98];姜黄素能诱导 $CD4^+$ T 细胞向 $CD4^+$ $CD25^+$ $Foxp3^+$调节性 T 细胞及分泌 IL-10 的Ⅰ型调节性 T 细胞分化,促进肠固有层分泌 TGF-β 和视黄酸,激活肠上皮细胞及 ILC 分泌 IL-25、IL-33、IL-22 和 IL-17,抑制肠道炎症[99-100];黄芩苷能调节肺、肠黏膜 sIgA 分泌水平及 $CD4^+/CD8^+$淋巴细胞比例,改善轮状病毒诱导的肺、肠病理损伤[101]。

同时,中药对化疗及创伤致肠黏膜免疫损伤也有保护作用。生姜泻心汤(生姜、大枣各 12 g,党参、黄芩、半夏、甘草各 9 g,干姜、黄连各 3 g)通过上调伊立替康化疗后大鼠肠黏膜 $CD4^+$和 $CD8^+$T 淋巴细胞数及 sIgA 水平,改善肠黏膜免疫屏障功能,从而预防伊立替康诱导的迟发性腹泻[102];芪黄煎剂(黄芪、党参、白术各 20 g,丹参 15 g,黄芩 12 g,大黄、枳实、厚朴各 10 g)能促进胃切除术后大鼠小肠黏膜免疫屏障 IgA^+B 淋巴细胞和 $CD3^+$、$CD4^+$、$CD8^+$T 淋巴细胞增殖、分化及 sIgA 分泌[103],上调肠淋巴细胞表面归巢受体 α4β7、L 选择素和淋巴细胞功能相关抗原 1(LFA-1)阳性细胞数量及 mRNA 相对表达量[104],增加肠淋巴细胞归巢 T、B 细胞数量[105],减轻创伤后肠道免疫屏障功能损伤。

5 结 语

“肺与大肠相表里”理论自建立以来,与临床应用互动发展。在该理论指导下,中医药在严重急性呼吸综合征(SARS)[106]、2019 冠状病毒病[18,107]等传染病的防治中发挥了重要作用。邱海波教授在介绍 2019 冠状病毒病中西医结合治疗经验中也提到“肺与大肠相表里”的中医原理,并指出了该理论与现代医学的共通之处[108]。随着中医理论和现代医学关联性的深入分析,“肺与大肠相表里”理论或可指导西医临床肺、肠相关疾病的治疗。

现代药理研究表明,肺、肠黏膜中的趋化因子、归巢受体、sIgA、$CD4^+$、$CD8^+$T 淋巴细胞及肺、肠道微生物等可能为"肺与大肠相表里"的物质基础,而肺、肠黏膜间 ILC 及树突状细胞等免疫细胞的迁移、归巢及其介导的炎症反应是肺-肠之间病理传变的主要机制。现有研究已证实补益类、清热解毒类中药复方及其有效部位和活性成分可通过增加黏膜上皮淋巴细胞和杯状细胞数使黏膜屏障结构趋于完整、促进黏膜 sIgA 分泌及淋巴细胞归巢等,对肺、肠黏膜免疫功能异常介导的相关疾病具有较好疗效。但现有研究主要关注于 sIgA、细胞因子表达水平及 ILC 等免疫细胞数量的变化,而对与之相关的气道/肠道黏液高分泌、肺及肠道黏膜屏障免疫细胞功能改变、肺-肠黏膜免疫相互作用动态过程及肺/肠局部微生态的干预作用等的研究相对较少;此外,关于清热解毒类中药和补益类中药对肺、肠黏膜免疫调节作用的异同点、所治疾病的特点及其特征作用机制,也未有相关的比较研究。上述未解之处可作为"肺肠同治"中药后续研究的方向之一。

中医药是我国具有原创优势的科技资源,是提升我国原始创新能力的"宝库"之一。"肺与大肠相表里"理论历久弥新,对肺-肠黏膜屏障的差异性、现代疾病过程中肺-肠道黏液高分泌与传统肺与大肠"津液相求"理论及其与黏膜免疫调节间的相关性的深入研究,以及"肺肠同治"确有疗效的清热解毒类中药和补益类中药及复方所具有的清热解毒、补益功效与其调节肺-肠黏膜免疫作用间的相关性和生物学基础的阐明,将有助于促进"肺与大肠相表里"理论现代科学内涵的阐释,使其在一些新发、难治疾病的防治中发挥更大的作用。

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