中医药在新型冠状病毒肺炎炎症损伤中的作用研究进展

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摘要 新型冠状病毒肺炎(NCP)是一种由COVID-19引起的感染性呼吸道疾病。炎症风暴(也称为细胞因子风暴)在COVID-19诱导的肺损伤中起重要作用, 并且是导致NCP患者病情加重甚至死亡的核心病理因素。促炎性细胞因子的过度表达和释放将导致组织损伤。研究表明, 对炎症损伤的干预可能是中医药治疗NCP的重要机制之一。临床研究发现, 对NCP患者进行中医药早期干预可以显著缓解体征和症状, 缩短病程, 降低患者进入严重期的可能性, 并降低病死率。通过对《新型冠状病毒肺炎诊疗方案(试行第八版)》及已发表文献的分析发现, 中医药对NCP患者炎症损伤的调控通过多靶点实现。一方面, 一些中药对病毒的增殖具有直接作用; 另一方面, 某些中药通过调节免疫细胞的功能, 减少促炎细胞因子的产生, 同时增加抗炎介质的分泌而重构机体免疫平衡。NCP的流行尚未结束, 世界仍在遭受COVID-19病毒的攻击。本文旨在综述中医药对COVID-19诱导的炎症反应的作用及其机制, 以期临床和科研工作者提供资料帮助。

关键词 新冠肺炎, 炎症风暴, 中医药, 研究进展

新型冠状病毒肺炎(novel coronavirus pneumonia, NCP), 简称“新冠肺炎”, 是指2019新型冠状病毒感染导致的传染性强的呼吸系统疾病。截至2021年3月份, WHO(World Health Organization)公布的数据显示, 全世界已经有超过一亿例新型冠状病毒的确诊患者, 死亡病例更是超过259万(<https://covid19.who.int/>)。病毒感染后尽管部分患者表现为无症状感染, 仍有部分患者会有肺炎的情况发生, 甚至会有超过10%患者病情加重, 需要机械通气支持治疗^[1]。新冠肺炎初期患者常以发热、干咳、头痛、乏力、腹泻、纳差等为主要临床表现, 重症患者则可能出现急性呼吸窘迫综合征(acute respiratory distress syndrome, ARDS)或多系统器官功能衰竭(multiple organ dysfunction syndrome, MODS)^[2], 危

及生命。因此, 早期诊断、早期干预、降低重症发生率是新冠肺炎治疗的关键环节。

大量临床及基础研究发现, 炎症风暴是导致新冠肺炎患者病情加重甚至死亡的核心病理因素^[3-5]。炎症风暴又被称为细胞因子风暴, 主要体现为促炎的细胞因子过度表达、释放, 导致自身攻击和侵略性的炎症反应, 从而引起ARDS或者MODS等, 这也是新冠肺炎患者预后不良的主要原因之一^[6]。中医药在新冠肺炎治疗中的积极作用已得到初步临床证实^[7], 大量文献也对潜在的机制进行了研究报道。本文通过检索国内外已发表的相关文献, 试图揭示中医药调节新冠肺炎炎症损伤的科学内涵, 为其临床应用提供参考。

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1 目前对炎症风暴的认知

1.1 诱发炎症风暴的机制

目前研究已证实并得到公认: 尽管炎症因子在病毒感染后可以起到重要的免疫作用, 但是过度的免疫反应将会对人体造成伤害^[8], 甚至引起ARDS, 对患者可造成不可逆转的损伤^[9].

体外实验证明, SARS-COV进入单核细胞分化的树状细胞后, 白介素(IL)-12、IL-6、肿瘤坏死因子(TNF)- α 等炎症因子和趋化因子等表达显著增加^[10]. 研究发现, 新冠肺炎重症患者体内T细胞活化最为明显^[11]. IL-12等可调节CD4⁺ T细胞分化、激活1型T辅助细胞(Th1), 介导细胞免疫, 细胞因子分泌突破阈值而失控, 最终形成免疫风暴^[12]; IL-6和TNF- α 可以对细胞的增殖、分化、炎症、凋亡产生作用^[13]. 此外, 自然杀伤细胞(NK)在感染后释放的大量细胞因子, 如NK细胞毒性因子(NKCF)、肿瘤坏死因子(TNF)等, 对靶细胞也具有直接杀伤作用. ARDS正是非特异性炎性细胞浸润及炎症因子释放引起的肺和间质组织损伤的结果, 在此过程中, 炎症风暴起了决定性作用.

除炎症因子外, 血管紧张素转换酶2(ACE2)在新冠肺炎炎症损伤中的作用也引起临床医生及药理学家们的关注. 正常情况下, 肾素-血管紧张素-醛固酮系统(RAAS)通过调节体液量, 协调酸碱平衡来维持机体内部的稳态^[14]; 而ACE2对RAAS系统起重要的调节作用^[15]. 研究发现, SARS-COV-2通过与ACE2结合进入

以II型肺泡上皮细胞为主的宿主细胞, 最后导致宿主的感染^[16]. 研究发现, ACE2在病毒的影响下表达下调, 血管紧张素II(Ang II)随之升高, 激活了RAAS, 也可生成大量的免疫因子^[12], 如可溶性IL-6, 进一步加强了炎症反应^[17], 加剧靶器官损伤^[18]. 由于受体ACE2在人体组织分布范围较广, 在血管内皮细胞中广泛表达, SARS-COV-2病毒感染内皮细胞后, 可引起广泛性微血管功能障碍和组织缺血^[19], 这可能是病毒诱发患者全身器官受损甚至衰竭的重要原因^[20]. 在另一方面, ACE2表达随着年龄的增长而呈增加趋势, 而ACEI类药物在老年人群应用更为广泛, 这也可能是老年患者的病情较其他人群更为严重的原因之一^[21](图1).

1.2 中医对炎症风暴的解释

炎症损伤是加剧新冠肺炎患者死亡的主要原因之一^[3]. 研究发现, 中医药参与治疗的患者治愈率较纯西医治疗有显著提升^[22]. 在湖北省疫情防控工作新闻发布会上, 黄璐琦院士指出, 中西医结合治疗组相比西医组, 核酸转阴及平均住院时间明显缩短, 咳嗽、发热等症状也得到了明显改善, 显示其可能的重要作用机制是调节机体炎症平衡(<http://bgs.satcm.gov.cn/gongzuodongtai/2020-02-15/13088.html>). 在国家卫生健康委员会最新发布的《新型冠状病毒肺炎诊疗方案(试行第八版)》(以下简称第八版诊疗方案)中, 提到本病属于中医“疫”病范畴, 病因为感受“疫戾”之气^[23]; “戾气”具有极强的传染性及流行性, 且易夹带湿、热、瘀、毒

图1 新型冠状病毒诱发炎症风暴是诱发靶器官损伤的关键

Figure 1 COVID-19 virus-induced inflammatory cytokine storm plays pivotal role in target organ injury

等邪,疫毒侵袭人体,损伤正气,对平素体质虚弱或在重症和危重型阶段的患者,体内正气不足,不能鼓邪外出,血液和津液运化失职,痰瘀内生,郁久化热,热毒即生,诸邪通过三焦弥漫全身,充斥表里、内外,可造成全身多脏器损害^[24]。“炎症风暴”最终导致患者出现多脏器衰竭的临床特征即与之相似。因此,肺部急性炎症病因的中医理解,或可用“热毒”来类比解读^[25]。

2 中医药对炎症风暴的调节

2.1 中医药对传统病毒感染性疾病炎症损伤的调节作用

截至目前,中药对一般病毒感染所致炎症损伤作用的机制研究还主要集中于非特异性抗炎作用。有研究发现,青蒿琥酯可以抑制促炎作用的PI3K/Akt通路和p44/42 MAPK信号通路,同时减轻脂多糖(LPS)诱导的IL-6和IL-8炎症损伤^[26]。白藜芦醇和大黄素等可以通过抑制肺组织中的NF- κ B和PI3K等信号通路活化缓解呼吸道合胞病毒(RSV)感染的肺炎小鼠体内的炎症反应,减少细胞因子的释放^[27,28],改善ARDS^[29]。而感染了流感病毒的小鼠在经过栀子的提取物栀子苷治疗后,IL-6和TNF- α 的表达显著降低,Toll样受体3(TLR3)以及干扰素 β 结构域的TIR衔接蛋白(TIRF)表达被显著抑制,并发症减少^[30]。有理由相信,众多中药活性成分很可能以类似的方式发挥抗新冠肺炎炎症损伤的作用。

2.2 中医药对COVID-19导致的炎症损伤干预作用

针对新冠肺炎引起的炎症风暴重症患者的治疗,目前主要采取体外血液净化技术,人工肝(ALSS)联合体外膜肺氧合技术(ECMO)也是较为有效的治疗方式之一^[31],而中医药及早参与治疗则可显著提升临床缓解率^[22]。针对COVID-19的中医药治疗策略,主要从免疫抑制和抗炎这两个方向进行考量。

“三方三药”是中医药治疗新冠肺炎的代表性方案,包括清肺排毒汤、化湿败毒方、宣肺败毒汤、金花清感颗粒、连花清瘟胶囊、血必净注射液。清肺排毒汤为临床治疗期的通用方剂,治以宣肺透邪、清热化湿、健脾化饮,适用于新冠肺炎轻型、普通型、重型患者,在危重症患者的救治中也可根据患者自身情况酌情使用^[23]。研究认为,清肺排毒汤在COVID-19治疗中的关键作用机制可能与其化合物直接干扰Toll样受体并调节下游信号通路介导的炎症因子表达有

关^[32]。徐天馥等人^[33]运用网络药理学方法分析清肺排毒汤,发现槲皮素、黄芩素、柚皮素、木犀草素、山奈酚等可能是主要的活性成分,具有不同程度的抗炎、抗病毒等功效,并可通过调节IL-17、TNF、MAPK等相关信号通路调节细胞的抗炎反应,降低免疫损伤。化湿败毒方中的槲皮素、黄芩素、汉黄芩素、黄芪甲苷等活性成分,可能通过抑制新型冠状病毒的侵染、复制、增殖,调节炎症反应,有效阻断炎症风暴的形成^[34]。宣肺败毒汤也可通过黄酮类和植物甾醇类活性成分调节IL-6、MAPK1、MAPK3、NOS2、CCL2、EGFR、IL-1 β 等关键靶点,抑制病毒的入侵及复制,发挥其抗炎症风暴、调节机体免疫的作用^[35]。毛昀等人^[36]运用网络药理学研究方法发现,金花清感颗粒的作用靶点可能是IL-6、TNF等免疫炎症因子。目前临床推荐的连花清瘟胶囊则主要通过抑制病毒复制,以浓度依赖的方式在mRNA水平上显著减少促炎细胞因子(TNF- α 、IL-6、CCL-2/MCP-1和CXCL-10/IP-10)的产生,发挥其抗冠状病毒作用^[37]。Chen等人^[38]发现,血必净注射液显著降低了败血症小鼠的TNF- α 和IL-6水平,可通过预防炎症风暴,抑制炎症反应,调节Tregs和Th17细胞的平衡来提高小鼠的存活率。尽管目前中药治疗新冠肺炎的机制研究有限,但综合上述研究发现,除非特异性抗炎作用外,中药抑制病毒增殖也可能是关键机制之一。

3 中医药对新冠肺炎不同病情患者的应用差异性

在第八版诊疗方案中,根据疾病的发展阶段和中医药治疗建议,将新冠肺炎分为医学观察期、临床治疗期和恢复期,在临床治疗期又根据病情的轻重分为轻型、普通型、重型、危重型4型^[23]。

3.1 医学观察期

此期炎症风暴还未在体内大量形成,临床表现为乏力伴肠胃不适或伴发热,第八版诊疗方案中推荐的中成药为藿香正气胶囊、金花清感颗粒、连花清瘟胶囊、疏风解毒胶囊^[23],推荐选用的药物以清热解毒药、解表药、化湿药为主,功能主治疏风宣肺、清热解毒化湿。夏文广等人^[39]对52例新型冠状病毒肺炎患者的临床资料进行回顾性分析发现,中西医结合组的临床治愈率明显高于西药组,普通型转重症发生率及危重型发生率均低于西药组,说明在早期运用中医药

介入治疗, 或可减缓或阻断炎症风暴在体内的爆发。

3.2 临床治疗期

临床治疗期是指患者已确诊新冠肺炎的阶段, 此时“炎症风暴”达到高峰, 促炎的细胞因子大量生成, 导致机体发生过度的免疫反应, 是治疗的难点和重点。此期湿毒易侵袭脾肺, 致人体内生诸邪, 正气虚损。

3.2.1 轻型/普通型/重型

轻型患者处于疫毒初起阶段, 以发热、乏力、周身酸痛、咳嗽、咯痰等为主要临床表现, 证型包括寒湿郁肺证、湿热郁肺证; 普通型患者此期以湿毒郁肺证和寒湿阻肺证为主, 患者多无呼吸困难、脉微欲绝等征象; 重型患者则可出现气促、大热、吐血等症状, 病机仍以热毒和湿毒为主^[40]。以上各证型虽在临床表现上有所不同, 但都属于正气对侵袭人体的“疫戾”之气奋力抗争所产生的结果。此期病情发展迅速, 使用的药物以化湿药、清热解毒药、解表药、利水药为主。何黎黎等人^[41]通过对各地区“诊疗方案”的统计分析, 总结出甘草、丹参、黄芩、桔梗、金银花五味中药使用频次最高。研究发现, 甘草可减轻由过度免疫反应所导致的肺部损伤; 张剑锋等人^[42]临床研究发现, 给急性肺损伤患者注射甘草酸二铵, 可促进抗炎因子IL-10的分泌, 抑制体内TNF- α 表达。动物实验发现, 丹参对急性肺损伤的小鼠有保护作用, 其作用机制与抑制TLR-4/NF- κ B介导的炎症相关^[43]。桔梗皂苷和汉黄芩素已被广泛证实具有抗体内炎症、抗脂质过氧化和下调肺组织中NF- κ B蛋白等非特异性抗炎作用^[44,45]。奚清^[46]探讨金银花在免疫调节过程中对细胞因子的影响机制发现, 其在一定程度上可抗流感病毒性肺炎, 这与金银花提取物调控免疫细胞因子TNF- α 和IL-1 β 表达有关。

3.2.2 危重型

危重期是机体与病邪作最后抗争的阶段, 炎性物质的大量产生造成全身多脏器损害。此期属于内闭外脱证, 是热陷心包证的进一步发展, 是由气营两燔向功能衰竭转化的过程中所形成的危重症。推荐处方为人参、黑顺片、山茱萸, 送服安宫牛黄丸或苏合香丸。现代药理研究表明, 人参多糖在炎症及免疫抑制情况下可增强免疫活性^[47]。黑顺片(附子)回阳救逆、补火助阳、散寒止痛。张海东^[48]通过给脓毒症大鼠模型附子药液灌胃, 观察其对炎症反应及免疫功能的调节, 发现附子可降低大鼠血浆中促炎因子IL-1和TNF- α 的表达

水平。山茱萸总苷及多糖可降低心肌组织中炎症因子IL-6的表达, 而对抗炎因子IL-10的表达则有促进作用^[49]。安宫牛黄丸由牛黄、犀角、麝香、珍珠、朱砂、雄黄、黄连、黄芩、栀子、郁金、冰片等11味中药组成, 具有清热解毒、开窍醒神的作用。Fan等人^[50]通过动物实验发现, 安宫牛黄丸可调节Th17/Treg平衡, 抑制促炎介质IL-6的释放, 促进抗炎因子IL-10的生成, 减少炎症细胞浸润; 此外, 小剂量的安宫牛黄丸具有抗炎作用, 大剂量则具有免疫调节作用, 这与下调IFN- γ 、CCL5和CCR5的mRNA表达水平有关。

3.3 恢复期

此期肺部炎症尚未完全消除, 各脏腑组织器官功能有待恢复。该期证型以肺脾气虚证和气阴两虚证为主, 患者处于疫毒将除、正气未复的时期, 除乏力、气短等肺系表现外, 还会出现纳差等脾胃系统症状, 同时相关检测指标亦未恢复正常。该期病性以虚为主, 余邪未尽, 古人云“正气存内, 邪不可干”, 此期应以扶正补益为主, 清除余邪, 提高机体对炎症风暴的耐受性, 减少全身各脏器的损害^[51]。

4 总结与展望

中医药治疗传染性非典型肺炎(SARS)的疗效已得到世界卫生组织肯定^[52,53]。在本次抗击新冠肺炎疫情中, 中西医结合治疗同样发挥了重要作用。在全球新冠肺炎快速蔓延的今天, 中医药在防治方面取得的成效获得了国际社会的持续关注(http://paper.people.com.cn/rmrbhwb/html/2020-04/27/content_1983884.htm)。目前针对炎症风暴, 西医多采用免疫治疗、呼吸支持、糖皮质激素治疗、血液净化治疗、体外膜肺氧合等联合治疗方法, 在一定程度上降低了病死率; 临床及基础研究已显示(图2), 中医药早期干预, 可有效抑制炎症损伤、缓解患者症状、缩短发热时间和病程、降低轻型和普通型患者向重型发展的几率、提高治愈率、降低病死率、减轻后遗症^[54]、促进恢复期人群机体康复^[55]。

目前疫情尚未结束, 全球仍处在COVID-19病毒的侵袭中。尽管以往研究发现, 中药的某些成分, 如黄芪素、黄芪甲苷、桔梗皂苷和汉黄芩素等, 以及中药复方清肺排毒汤、化湿败毒方等都可以对炎症因子起到控制的作用, 但它们具体作用机制和关键效应物质基础仍有待深入研究。在另一方面, 中医药对不同证型患

图 2 (网络版彩色)中医药多靶点调控新冠病毒引起的炎症损伤

Figure 2 (Color online) Multi-target effects of Traditional Chinese Medicine against COVID-19 induced inflammatory injury

者精准用药的客观指标仍有待进一步明确,以利临床工作中推广。中西医结合已证实可更有效抑制疾病发展,但中医药在中西医结合治疗中扮演的角色以及科学内涵仍有待进一步挖掘。尽管中医药对COVID-19病

毒作用的中、西医研究仍有大量工作需要开展,但中医药早期介入的优势已得到临床验证。本文阐述中医药在此次新冠肺炎中对炎症损伤的作用,旨在为中医药干预新冠肺炎临床和科研工作提供参考。

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Summary for “中医药在新型冠状病毒肺炎炎症损伤中的作用研究进展”

Progress on the role of Traditional Chinese Medicine in inflammatory injury of COVID-19

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Novel coronavirus pneumonia is an infectious respiratory disease induced by a novel coronavirus, named COVID-19. At present, novel coronavirus pneumonia is widely spread around the world, with the characteristics of long incubation time, strong contagion, rapid progress, and high fatality rate. Inflammatory storm, also known as cytokine storm, has been found to play an important role in COVID-19 induced lung injury, and is believed to be one of the core pathological factors leading to exacerbation and even death of novel coronavirus pneumonia patients. It is found that over-expression and release of pro-inflammatory cytokines such as IL-6 will lead to self-attack and aggressive inflammatory response, and finally cause tissue damage. Studies have shown that the intervention of inflammatory injury may be one of the important mechanisms that contribute to therapeutic effect of Traditional Chinese Medicine against COVID-19. Clinical studies found that early intervention with Traditional Chinese Medicine in novel coronavirus pneumonia patients could significantly alleviate signs and symptoms, shorten course of the disease, decrease possibility of the patients progressing into severe stage, slow or even block the outbreak of inflammatory storm in the patient's body, improve cure rate, reduce mortality, relieve sequelae, and promote the recovery of the patients in the recovery period. Through analyzing the representative prescription of *Traditional Chinese Medicine in the Eighth Edition of the Diagnosis and Treatment Scheme for COVID-19*, we found the regulation on the inflammatory injury by Traditional Chinese Medicine is realized in a multi-target manner. On the one hand, some Chinese Medicines are exhibited with direct effects against proliferation of the virus; on the other hand, some Chinese Medicines are shown with ability to re-balance the immune system via regulating function of immune cells, decreasing production of pro-inflammatory cytokines while increasing secretion of anti-inflammatory mediators. The epidemic of novel coronavirus pneumonia has not yet ended, and the world is still under the attack of COVID-19 virus. Although previous studies have found that certain ingredients in Traditional Chinese Medicine, such as astragaloside IV, platycodin and wogonin, etc., as well as Traditional Chinese Medicine prescription including Qingfei Paidu Decoction, Huashibaidu Decoction, etc., can control inflammatory injury, their specific mechanism and the material basis still need to be studied in depth. On the other hand, the objective indicator of Traditional Chinese Medicine for patients with different syndromes still needs to be further clarified to facilitate its promotion in clinic. The integration of Traditional Chinese Medicine and western medicine has been proved to be more effective in inhibiting the development of novel coronavirus pneumonia, but the role of Traditional Chinese Medicine in the integrative therapy still needs to be further explored. Although there is still a lot of work to be carried out, the advantage of early intervention with Traditional Chinese Medicine against COVID-19 virus has been verified in both clinical and experimental studies. This paper aims to review mechanism and treatment strategy of Chinese Medicine on COVID-19 induced inflammation, and provide references for researchers in related area.

COVID-19, inflammatory storm, Traditional Chinese Medicine, research progress

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