

· 综述 ·

中药虎杖治疗脓毒症的研究进展

李响, 王杨, 葛晓利, 潘曙明

(上海交通大学医学院附属新华医院急诊医学科, 上海 200092)

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脓毒症是指因感染引起宿主反应失调, 导致危及生命的器官功能障碍^[1]。全球发病率高达 667.5/10 万人, 严重时可出现休克, 死亡率高达 46.4%^[2]。近年来, 虽然对脓毒症发病机制的研究不断深入, 治疗手段不断革新, 但仅少数治疗方法被证实能使患者获益, 如早期启用抗菌药物、早期足量液体复苏等^[3]。较新的治疗方法如粒细胞-巨噬细胞集落刺激因子 (granulocyte macrophage colony-stimulating factor, GM-CSF)、 γ 干扰素 (interferon γ , IFN- γ)、血栓调节蛋白 (thrombomodulin, TM)、亚甲蓝、轻度低温诱导等^[4]的具体疗效还有待进一步研究验证。脓毒症的治疗效果不理想主要因为其发病机制复杂, 涉及炎症和免疫反应过度激活及随后发生的免疫抑制^[5-8]、凝血功能紊乱^[9]、补体激活^[10]、内皮活化与损伤^[11-13]、氧化应激^[14]和细胞凋亡^[7]等多个方面, 单一针对某个靶点的治疗难以获得较理想的结果。脓毒症属中医“伤寒”“外感热病”“温毒”等范畴, 中医讲究阴平阳秘, 以辨证论治为指导, 治病求本, 以扶正祛邪、标本兼治为原则, 中药通常具有多靶点作用的特点。已有大量相关研究证实中药对于脓毒症的治疗作用^[15-17]。多项研究表明中药虎杖 (*Polygonum cuspidatum* Sieb. et Zucc.) 具有抗炎^[18]、抗氧化^[19]、调节免疫^[20]、抗血小板聚集^[21-22]、调节血脂^[23]、保护线粒体^[24]等作用, 有关虎杖对脓毒症治疗作用的研究也在不断增多。本文将综述虎杖对脓毒症治疗作用的相关研究进展及可能的作用机制, 为未来的研究提供依据和支持。

虎杖及其有效成分

虎杖为蓼科 (*Polygonaceae*) 蓼属 (*Polygonum*) 多年生灌木状草本植物, 以其干燥根茎入药, 其味微苦、性微寒, 归肝、胆、肺经, 具有利胆退黄、清热解毒、散瘀止痛、止咳化痰的功效^[25]。现代研究发现, 虎杖中主要含有蒽醌类 (大黄素、大黄酸、大黄酚等)、二苯乙烯类 (虎杖苷、白藜芦醇等)、黄酮类 (橙皮素、芦丁、槲皮素等)、香豆素类以及一些脂肪酸

类化合物^[26], 能通过抗炎、抗氧化、改善细胞连接、抗细胞凋亡等多种作用改善脓毒症预后^[27-28]。

虎杖的抗炎作用

在脓毒症发病早期, 病原体及其产生的毒素入血, 可刺激机体产生各种促炎因子如白介素 (interleukin, IL)-1、IL-6、肿瘤坏死因子 α (tumor necrosis factor α , TNF- α) 等, 研究发现, 核因子- κ B (nuclear factors- κ B, NF- κ B) 和促分裂原活化的蛋白激酶 (mitogen-activated protein kinases, MAPK) 是上述促炎因子的关键转录因子^[29]; 而脂多糖 (lipopolysaccharide, LPS) 可通过乙酰化作用, 使细胞内沉默信息调节因子 1 (silent information regulator 1, SIRT1) 与高迁移率族蛋白 B1 (high mobility group box protein 1, HMGB1) 解离, HMGB1 释放入血^[30], 促进促炎因子释放。早期炎症因子 TNF- α 、IL-6 和晚期释放的 HMGB1 相互促进, 形成炎症细胞因子风暴, 破坏凝血、免疫和黏膜屏障等系统, 最终引发致死性的脓毒性休克和多器官功能障碍 (multiple organ dysfunction, MODF) 综合征 (multiple organs dysfunction syndrome, MODS)^[31-33]。Wang 等^[34]的研究显示白藜芦醇既能通过磷脂酶 D (phospholipase D, PLD) 调控 Toll 样受体 4 (Toll-like receptor 4, TLR-4) 的下游信号分子鞘氨醇激酶 1 (sphingosine kinase 1, SphK1)、胞外信号调节激酶 1/2 (extracellular signal-regulated kinase 1/2, ERK1/2) 和 NF- κ B, 减少人原代单核细胞在 LPS 刺激下产生的细胞因子、趋化因子及 HMGB1, 也可通过下调髓样分化因子 88 (myeloid differentiation factor 88, MyD88), 抑制 LPS/Toll-4/NF- κ B 信号通路, 发挥抗炎作用。Shang 等^[35]发现白藜芦醇不但能降低大鼠心肌细胞 NF- κ B、TNF- α 、IL-6、IL-1 β 和 TLR-4 的表达水平, 还能明显抑制磷脂酰肌醇-3 激酶 (phosphatidylinositol 3-kinase, PI3K)/蛋白激酶 B (protein kinase B, AKT)/哺乳动物雷帕霉素靶蛋白 (mammalian target of rapamycin, mTOR) 信号通路, 白藜芦醇对大鼠心肌细胞 NF- κ B 信号通路的抑制作用是否与 PI3K/AKT/mTOR 有关联, 还有待进一步研究阐明。Xu 等^[36]的研究显示白藜芦醇可上调乙酰化 SIRT1 的表达, 促进 HMGB1 的氨基端赖氨酸残基去乙酰化, 抑制 HMGB1 的出核转移, 通过抑制巨噬细胞分泌 HMGB1 改善脓毒症大鼠的肝损伤;

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通信作者: 潘曙明 E-mail: shumingpan@aliyun.com

Wen 等^[37]发现虎杖中的大黄酚能抑制 LPS 诱导的 HMGB1 表达、核-质转移及其在巨噬细胞内的乙酰化,抑制 HMGB1 出胞,改善脓毒症急性肺损伤小鼠预后,具体机制可能与上调组蛋白脱乙酰化酶 3(histone deacetylase 3, HDAC3)的表达有关。

虎杖的抗炎作用还与其诱导特定巨噬细胞分化表型有关。巨噬细胞分为 2 种经典表型,LPS 或 IFN- γ 激活的 M1 型巨噬细胞主要产生细胞因子和炎性因子(IL-1 β 、IL-18、TNF- α 、IL-12),高表达诱导型一氧化氮合酶(inducible nitric oxide synthase, iNOS)、TNF- α 、趋化因子配体 9(chemokine ligand 9, CCL9)、CCL10 等 M1 型相关基因,促进炎症反应。IL-4、IL-10 和 IL-13 激活的巨噬细胞呈现出 M2 型极化表型,分泌大量 IL-10、转化生长因子 β (transforming growth factor β , TGF- β)等抗炎因子,高表达过氧化物酶体增殖物激活受体 γ (peroxisome proliferator-activated receptor γ , PPAR γ)、精氨酸酶 1(arginase1, Arg-1)、壳多糖样蛋白 3(chitinase-like protein 3, Chl3)和缺氧诱导型基因 FIZZ1 等,参与了组织重塑和修复^[38]。Saqib 等^[39]发现白藜芦醇可诱导巨噬细胞向 M2 型分化,从而抑制巨噬细胞促炎症因子分泌,上调抗炎因子表达,改善脓毒症预后;Ding 等^[40]发现大黄素也可通过促进小鼠巨噬细胞向 M2 型分化减轻脓毒症所致的肝功能损伤。

虎杖的抗氧化作用

越来越多的研究表明氧化应激在脓毒症发病中起重要作用。活性氧(reactive oxygen species, ROS)自由基和活性氮(reactive nitrogen species, RNS)自由基等氧化剂大量产生,抗氧化剂相对不足引发严重氧化应激损伤,导致血管通透性受损,线粒体功能障碍和心脏功能下降^[14, 41]。脓毒症时 iNOS 过量表达催化合成过量一氧化氮(nitric oxide, NO)^[42],既能直接对肾单位产生毒性作用,也可通过减低血管张力降低血压,使肾脏因灌注不足发生损伤^[43]。Aydin 等^[44]和 Zhang^[45]发现白藜芦醇和大黄素能降低脓毒症大鼠肺和肾组织 iNOS 和 NO 浓度,提高肺组织还原型谷胱甘肽/氧化型谷胱甘肽(glutathione/oxidized glutathione, GSH/GSSG)比值,提升过氧化氢酶(catalase, CAT)、超氧化物歧化酶(superoxide dismutase, SOD)等抗氧化酶活性,减轻脓毒症小鼠的脏器损伤;吴孟娇等^[46]的研究表明虎杖苷可通过抑制 iNOS mRNA 表达,减少 NO 产生和谷胱甘肽 S 转移酶-A1(glutathione S-transferase A1, GSTA1)分泌,显著减轻脓毒症小鼠近端肾小管损伤。

Kelch 样环氧氯丙烷相关蛋白 1(Kelch-like ECH-associated protein 1, Keap1)、NF-E2 相关因子 2(nuclear erythroid 2-related factor 2, Nrf2)和抗氧化响应元件(antioxidant response element, ARE)组成的 Keap1/Nrf2/ARE 信号通路是细胞内重要的抗氧化应激调控通路^[47],Wang 等^[48]和 Li 等^[49]发现白藜芦醇和虎杖苷均可通过增强 Nrf2 活性,促进血红素加氧酶 1(hemeoxygenase-1, HO-1)和谷氨酸半胱氨酸连接酶

(glutamate cysteine ligase, GCL)表达,减轻脓毒症氧化应激损伤。

虎杖的改善细胞连接作用

微血管内皮屏障改变后导致的血管渗漏与脓毒症器官功能障碍与高死亡率相关。内皮屏障主要由黏着连接(adherens junction, AJ)、紧密连接(tight junction, TJ)及两者与肌动蛋白(actin)骨架[β 连环蛋白(β -catenin)、p120 和斑珠蛋白(plakoglobin)]相互作用构成。血管内皮细胞 AJ 主要由血管内皮细胞上皮钙黏素(E-cadherin)、 β 连环蛋白和肌动蛋白细胞骨架构成。脓毒症时,LPS 通过抑制 SIRT3 介导 SOD2 去乙酰化,刺激线粒体产生大量 ROS,导致上皮钙黏素与 β 连环蛋白解离,AJ 破坏,内皮通透性增高^[50]。Wu 等^[50]发现虎杖苷可激活 SIRT3,介导 SOD2 的去乙酰化,减少 ROS 产生,稳定内皮 AJ,通过保护内皮通透性改善脓毒症小鼠预后。

肠道机械屏障的结构基础为上皮细胞间的 TJ,闭锁小带蛋白 1(zonula occludens protein 1, ZO-1)和闭锁蛋白(occludin)是肠上皮 TJ 的 2 个重要结构蛋白^[51]。上皮细胞及 TJ 构成了肠道物理屏障,该屏障的破坏参与了脓毒症 MODF 的发病过程,研究表明脓毒症大鼠结肠组织中 ZO-1 和闭锁蛋白的 mRNA 及蛋白表达水平下降,肠上皮 TJ 减少,肠道通透性增加^[52]。Li 等^[53]发现大黄素可通过调控肠黏膜 ZO-1 及闭锁蛋白表达,增强肠黏膜屏障功能,从而减少细菌移位,改善脓毒症所致的大鼠胃肠道功能失调。

星形胶质细胞通过分泌基质金属蛋白酶 9(matrix metalloproteinase 9, MMP-9)导致脑微血管内皮细胞间 TJ 破坏,血脑屏障通透性增加^[54],是脓毒症脑病(sepsis associated encephalopathy, SAE)发生发展的关键环节。刘新强等^[55]的研究表明白藜芦醇可能通过抑制大脑星形胶质细胞 MMP-9 表达,降低血脑屏障通透性,改善 SAE 大鼠预后。

虎杖的抗细胞凋亡作用

脓毒症会诱发脾脏、胸腺、淋巴结、内皮细胞、上皮细胞等器官免疫细胞广泛凋亡,免疫细胞(B 淋巴细胞、CD4⁺ T 淋巴细胞和树突状细胞等)大量丢失,极大增加患者发生继发性感染和院内感染的风险^[7]。研究表明脓毒症时机体可产生大量 RNS 和 ROS,导致线粒体膜通透性转换孔(mitochondria permeability transition pore, mPTP)呈持续高通透状态,细胞色素 C(cytochrome C, Cyt C)由此进入细胞质,激活胱天蛋白酶(caspase)级联反应,引起细胞凋亡^[56]。Wu 等^[50]发现虎杖苷可通过激动 SIRT3,促进亲环蛋白 D(cyclophilin D, CypD)去乙酰化,降低 mPTP 通透性,发挥抗细胞凋亡的作用^[50];Liu 等^[57]和 An 等^[58]发现白藜芦醇能通过激活 SIRT1 抑制脓毒症诱导的大鼠心肌细胞和肺泡上皮细胞凋亡,减轻脓毒症大鼠脏器损伤。

脓毒症仍然是全世界非常普遍、费用昂贵和致命的问题,作为涉及到多个系统功能紊乱的全身性疾病,其发病机

制及新治疗方法仍是临床研究的热点。近年来脓毒症结局得到显著改善,主要得益于早期快速识别和集束化治疗理念(足量液体复苏、使用有效抗菌药物等)的推广。迄今为止,尚未发现治疗脓毒症的特效药物,许多新治疗方法和药物在临床试验中均以失败告终。虎杖含有多种有效成分,目前针对蒽醌类(大黄素、大黄酸、大黄酚)和二苯乙烯类(虎杖苷、白藜芦醇)的研究较多,这些有效成分可在脓毒症治疗中发挥重要作用,能调控 TLR-4、MyD88、NF- κ B、PI3K/AKT、AKT/mTOR、SIRT1 等多种与炎症反应相关的关键信号分子,诱导巨噬细胞向特定的抗炎表型分化,通过减少炎症因子表达或促进抗炎因子产生发挥抗炎作用;能调节特定组织中 iNOS 和 NO 浓度以及 Keap1/Nrf2/ARE 信号通路,产生显著的抗氧化作用;能通过激活 SIRT3,调控 ZO-1、闭锁蛋白及 MMP-9 等蛋白等表达,改善细胞连接;能通过激活 SIRT3 发挥抗细胞凋亡作用。虎杖的其他有效成分如黄酮类、香豆素以及脂肪酸类对脓毒症是否也有治疗作用,尚有待进一步研究证实。脓毒症的发病机制涉及多条信号通路,虎杖的已知有效成分能否通过调节这些信号通路中的关键分子对脓毒症产生治疗作用仍然是主要的基础研究方向。此外,随着中医中药越来越被重视,作为一味经典中药材,虎杖与其他中药材依据中医辨证思想组成特定方剂,用于脓毒症的防治也将成为重要临床研究方向。

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