基于细胞因子风暴和中医“湿毒犯肺”理论挖掘抗新型冠状病毒肺炎中药

宗 阳[1,2,3], 姚卫峰[4*], 居文政[1*]

(1. 南京中医药大学附属医院, 江苏 南京 210029; 2. 南京中医药大学附属苏州市中医医院, 江苏 苏州 215009;
3. 苏州市吴门医派研究院, 江苏 苏州 215009; 4. 南京中医药大学药学院, 江苏 南京 210023)

摘要: 越来越多的临床证据表明, 新型冠状病毒肺炎 (COVID-19) 患者后期由于病情加重, 出现急性呼吸窘迫综合征和多器官衰竭等严重并发症而导致死亡, 而加重病情的原因主要是细胞因子风暴。针对COVID-19重症患者的治疗目前尚无特效药, 西药虽然可以改善部分症状但后遗症较大, 而中药在此次疫情中发挥了重要的作用。本文就临床报道的与细胞因子风暴相关的指标, 基于“湿毒犯肺”的中医理论通过中药系统药理学数据库和分析平台 (TCMSP) 挖掘并筛选作用于这些细胞因子的中药。结果发现, 主要包括白介素-6 (IL-6)、肿瘤坏死因子α (TNFα) 和粒细胞−巨噬细胞集落刺激因子 (GM-CSF) 等19个细胞因子与COVID-19密切相关, 麻黄、甘草和金银花等22种中药作用于这些细胞因子, 为中医临床治疗中后期COVID-19患者合理的选择处方以及加减用药提供一定的参考。

关键词: 细胞因子风暴; 新型冠状病毒肺炎; 湿毒犯肺; 中药

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Exploring the antiviral traditional Chinese medicine for the treatment of Coronavirus Disease 2019 based on the cytokine storm and Chinese medicine theory "damp toxin invading the lung"

ZONG Yang[1,2,3], YAO Wei-feng[4*], JU Wen-zheng[1*]

(*1. Affiliated Hospital of Nanjing University of Chinese Medicine, Nanjing 210029, China; 2. Suzhou TCM Hospital Affiliated to Nanjing University of Chinese Medicine, Suzhou 215009, China; 3. Suzhou Academy of Wumen Chinese Medicine, Suzhou 215009, China; 4. School of Pharmacy, Nanjing University of Chinese Medicine, Nanjing 210023, China*)

Abstract: More and more clinical evidence shows that patients with Coronavirus Disease 2019 (COVID-19) died due to severe complications such as acute respiratory distress syndrome and multiple organ failure due to the aggravation of the disease in the later period, and the main cause of the aggravation is "cytokine storm". There is no specific drug for the treatment of severe COVID-19 patients. Although western medicine can improve some symptoms, it leaves a large sequela, while traditional Chinese medicine plays an important role in this outbreak. In this paper, based on the clinical reported cytokines storm-related indicators, the traditional Chinese medicine systems pharmacology database and analysis platform (TCMSP) was used to mine and screen the traditional Chinese medicines acting on these cytokines based on the theory of "damp toxin invading the lung". It was found that 19 cytokines, including interleukin-6 (IL-6), tumor necrosis factor α (TNFα), granulocyte-macrophage colony stimulating factor (GM-CSF) and so on, were closely related to COVID-19, and 22 traditional Chinese medicines such

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*通讯作者 Tel: 86-25-86617141, E-mail: wzhju333@163.com;
Tel: 86-25-85811053, E-mail: yaowf@ njucm.edu.cn

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as *Ephedrae Herba*, *Glycyrrhizae Radix Et Rhizoma* and *Lonicerae Japonicae Flos* acted on these cytokines, so as to provide certain reference for the reasonable choice of prescription and addition or modification of drugs for COVID-19 patients in the middle and late stage of Chinese medicine clinical treatment.

Key words: cytokine storm; Coronavirus Disease 2019; damp toxin invading the lung; traditional Chinese medicine

截止2020年3月17日, 新型冠状病毒肺炎 (Coronavirus Disease 2019, COVID-19) 已造成中国8万余人确诊感染, 2千余例重症患者, 3千多人死亡[1], 并且该病毒已在全世界蔓延[2]。此次COVID-19造成的经济损失以及严重程度远远超过近几年发生的中东呼吸综合症 (Middle East respiratory syndrome, MERS) 和严重急性呼吸综合征 (severe acute respiratory syndrome, SARS)。Wang等[3]对138例住院新冠肺炎患者的数据分析显示, 新冠肺炎致死患者中性粒细胞增多, 可能与病毒入侵细胞时引起的细胞因子风暴 (cytokine storm, CS) 有关。近期的临床研究[3-5]分析了COVID-19患者的临床特征, 均发现肺炎患者, 特别是重症肺炎患者的淋巴细胞计数显著降低, 众多炎症因子如白介素-6 (IL-6) 和肿瘤坏死因子 (TNF) 等显著增高。事实上, 在SARS和MERS等病毒感染的后期, CS也是很多患者最终死亡的主要原因[6]。也就是说, CS始终是冠状病毒及其他严重感染患者疾病进展及死亡的重要推手之一。国家卫生健康委员会、国家中医药管理局最新印发的《新型冠状病毒感染的肺炎诊疗方案 (试行第七版)》(简称第七版诊疗方案) 显示[7], COVID-19患者以肺脏和免疫系统损害为主, 其他脏器因基础病不同而不同, 多为继发性损害。

CS即细胞因子释放综合征 (cytokine release syndrome, CRS), 又称高细胞介质症 (hypercytokinemia), 是由感染、药物或某些疾病引起的免疫系统过度激活, 体内的细胞因子平衡被打破, 促炎性细胞因子持续大量产生, 不断活化更多的免疫细胞聚集到炎症部位。过多的免疫细胞及多种促炎细胞因子会引起组织充血、水肿、发热和损伤, 还可能引起其他继发性感染甚至导致“全身炎症反应综合征”(脓毒败血症), 使患者因多器官衰竭而死亡[8]。魏海明团队[9]对33例新冠肺炎患者血液30项免疫学指标的全面分析, 发现了新型冠状病毒感染致重症肺炎CS关键机制: 新型冠状病毒感染后, 迅速激活病原性T细胞, 产生粒细胞−巨噬细胞集落刺激因子 (granulocyte-macrophage colony stimulating factor, GM-CSF) 和IL-6等因子。GM-CSF进一步激活$CD14^+CD16^+$炎症性单核细胞, 产生大量的IL-6和其他炎症因子, 从而形成炎症风暴, 导致严重的肺部和其他器官的免疫损伤 (图1)。因此, IL-6和GM-CSF是引发新冠肺炎患者CS的两个关键炎症因子。

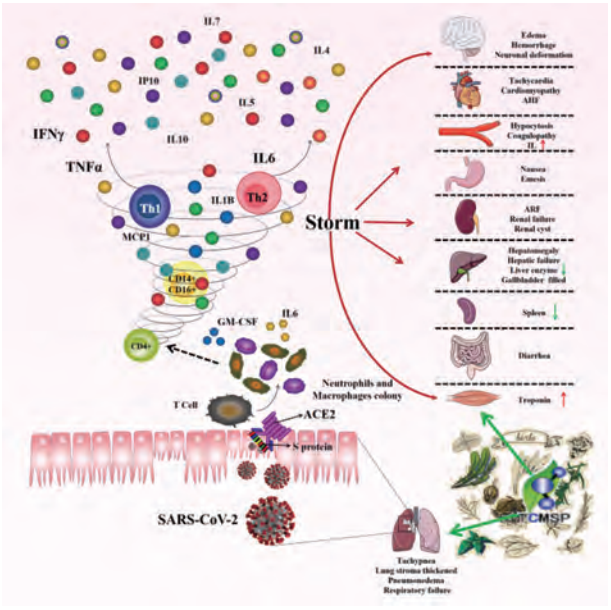

Figure 1 A hypothetical cytokine storm caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) invasion invading the lung and multiple organ failure induced by Coronavirus Disease 2019 (COVID-19) and the intervention of the traditional Chinese medicine systems pharmacology database and analysis platform (TCMSP) database. AHF: Acute heart failure; ARF: Acute renal failure; IL: Interleukin

目前, 针对CS治疗, 第七版诊疗方案采用糖皮质激素作为免疫抑制剂, 用于遏制重症患者的免疫激化反应, 但是糖皮质激素的使用可能会造成二次感染、病程延长等不良反应, 且存在严重后遗症风险[10]。诊疗方案中增加了血液净化对重型、危重型患者清除炎症因子, 阻断CS, 从而减轻炎症反应对机体的损伤。由此可见, 针对CS进行对症治疗或将成为重症患者的一线希望。中医认为COVID-19属于“疫病”范畴, 源于感受疫疠之气、湿毒犯肺, 基本病机特点为“湿、热、毒、瘀、虚”[11]。既往的药理学研究[12]表明, 中药在清除抗原、调节免疫和保护组织等方面都发挥着重要作用, 且中医药被广泛用于此次COVID-19的治疗中, 本文将针对临床报道的与CS相关的生化指标, 通过中药系统药理学数据库和分析平台 (TCMSP) 挖掘作用于细胞

因子的中药, 为临床选方、加减用药以及新药开发提供参考。

材料与方法

资料来源　以COVID-19、Coronavirus Disease 2019、2019-nCoV、2019 Novel Coronavirus、CS 和临床特征 (clinical characteristics) 组合检索中国知网和 PubMed 等数据库中相关信息, 纳入有关 COVID-19 患者的细胞因子相关的临床研究文献, 截止日期为 2020 年 3 月 17 日下午 17 点。

数据库和软件　数据库包括 TCMSP[13] (http://tcmspw.com/tcmsp.php, 版本: 2.3)、人类基因数据库 (Gene Cards)[14] (https://www.genecards.org, 版本: 4.13)、蛋白质靶点数据库 (Uniprot)[15] (https://www.uniprot.org) 和功能蛋白关联网络数据库 (STRING)[16] (https://string-db.org, 版本: 11.0); 分析软件包括网络分析工具 (Cytoscape)[17] (版本: 3.7.2)。

中药成分收集　借助 TCMSP, 以搜集到的相关细胞因子为关键词检索作用于细胞因子的中药及单体化合物。

靶点–网络的构建　运用 STRING 数据库分析细胞因子作用靶点之间关系进而使用 Cytoscape 进行可视化分析, 通过度 (Degree) 值大小评价 PPI 网络中蛋白质关系强弱。

初步验证　将数据库筛选得到的中药结合目前诊疗方案中所用的中药交集, 得出共性中药, 再通过文献检索各味中药作用于细胞因子的既往实验研究从而佐证本结果的合理性。

结果

1　COVID-19 相关的细胞因子的收集

截至 3 月 17 日, 共检索得到与 COVID-19 相关的细胞因子 19 个, 比 SARS (10 个) 和 MERS (4 个) 多, 见表 1[4,5,9,18-23]。由此可见, 本次的新冠病毒更容易激发 CS, 且涉及的细胞因子更广泛, 更容易导致人体的多器官衰竭。

2　靶点确认和中药筛选

将上述得到的 19 个细胞因子通过 Uniprot 校正基因名, 在 TCMSP 数据库搜索作用于 19 个细胞因子的中药, 发现多种中药作用于同一个细胞因子, 见表 2。分析该部分数据发现, 中药多成分治疗疾病是通过多靶点发挥疗效的, 且针对特定的细胞因子合理的加减用药, 以及优化处方可能会增强中药复方治疗新冠肺炎的疗效。

3　细胞因子之间的相互作用关系

将查询得到的 19 个靶点带入 STRING 数据库, 结果发现 19 个靶点的度值并没有明显的差异, 故采用数据库中的拓展功能将靶点相互作用网络拓展 10 次。通过 Cytoscape 软件中可视化 (图 2)。细胞因子作用靶点相互作用网络拓扑学分析, 见表 3 (度值 ⩾ 70)。经 Network Analyzer 分析网络拓扑学属性发现, 靶点相互作用网络包含 109 个节点、2 419 条边, 其中节点表示靶点, 每条边则表示靶点与靶点之间的相互作用关系, 靶点越大表示关联度越强, 其中平均节点度为 44.39, 从中可以发现 TNF 和 IL-6 在网络中占主导作用。

4　作用于细胞因子的交集中药

网络药理学表明, 中药可以通过多成分、多靶点和多途径发挥药效作用。由于作用于后 8 种细胞因子的中药太少 (表 2), 因此取作用于前 11 个细胞因子的中药求交集, 结果发现共有 62 种中药作用于 11 个细胞因子 (图 3); 再结合 2015 版《中国药典》记录的归肺经的标准进行筛选, 结果共得到包括麻黄在内的 22 种中药 (表 4)。

5　交集中药作用于细胞因子的既往实验总结

Wang 等[24]对新型冠状病毒肺炎中医药诊治方案综合分析得出, COVID-19 进展期多为“湿郁化热, 热毒损肺”, 治疗上以宣肺通腑、清热解毒为主, 攻下泻热以助肺气宣降。本文筛选得到的 22 种中药中麻黄、甘草、金银花、连翘和虎杖在新型冠状病毒肺炎诊疗方案的推荐处方中, 其作用于细胞因子的既往实验研究见表 5[25-33]。

Table 1　Changes of cytokine storm index caused by coronavirus. SARS-CoV: Severe acute respiratory syndrome coronavirus; MERS-CoV: Middle East respiratory syndrome-related coronavirus; IFNγ: Interferon gamma; IP-10: Interferon gamma-induced protein 10; MCP1: Monocyte chemotactic protein-1; TNFα: Tumor necrosis factor α; Basic FGF: Basic fibroblast growth factor; GCSF: Granulocyte colony stimulating factor; GM-CSF: Granulocyte-macrophage colony-stimulating factor; MIP1A: Macrophage inflammatory protein 1 alpha; PDGF: Platelet derived growth factor; VEGF: Vascular endothelial growth factor

Virus (year)	Related cytokine indicator	Reference
SARS-CoV (2003)	IL-1α, IL-1β, IL-8, IL-6, IL-10, IL-12, IFNγ, IP-10, MCP1, TNFα	[18–20]
MERS-CoV (2012)	IFNγ, TNFα, IL-15, IL-17	[21]
SARS-CoV-2 (2019)	Basic FGF, GCSF, GM-CSF, IFNγ, IL-10, IL-1RA, IL-1β, IL-2, IL-6, IL-7, IL-8, IL-9, IP-10, MCP1, MIP1A, MIP1B, PDGF, TNFα, VEGF	[4, 5, 9, 22, 23]

Table 2 Basic information of 19 cytokines and the role of traditional Chinese medicine (TCM). TCMSP: Traditional Chinese medicine systems pharmacology database and analysis platform

No.	Gene symbol	Uniprot official name	TCMSP protein name	Number of TCM
1	TNFα	TNF	Tumor necrosis factor	430
2	IL-10	IL-10	Interleukin-10	372
3	IL-6	IL-6	Interleukin-6	337
4	VEGF	VEGFA	Vascular endothelial growth factor A	304
5	IL-1β	IL-1B	Interleukin-1 beta	288
6	IL-2	IL-2	Interleukin-2	282
7	IFNγ	IFNG	Interferon gamma	260
8	IL-8	CXCL8	Interleukin-8	260
9	MCP1	CCL2	C-C motif chemokine 2	220
10	IP-10	CXCL10	C-X-C motif chemokine 10	188
11	GM-CSF	CSF2	Granulocyte-macrophage colony-stimulating factor	111
12	MIP1A	CCL3	C-C motif chemokine 3	23
13	basic FGF	FGF2	Basic fibroblast growth factor	14
14	PDGF	PDGFB	Platelet-derived growth factor subunit B	3
15	MIP1B	CCL4	C-C motif chemokine 4	2
16	GCSF	CSF3	Granulocyte colony-stimulating factor receptor	1
17	IL-1RA	IL1RN	Interleukin-1 receptor antagonist protein	1
18	IL-7	IL-7	Interleukin-7	0
19	IL-9	IL-9	Interleukin-9	0

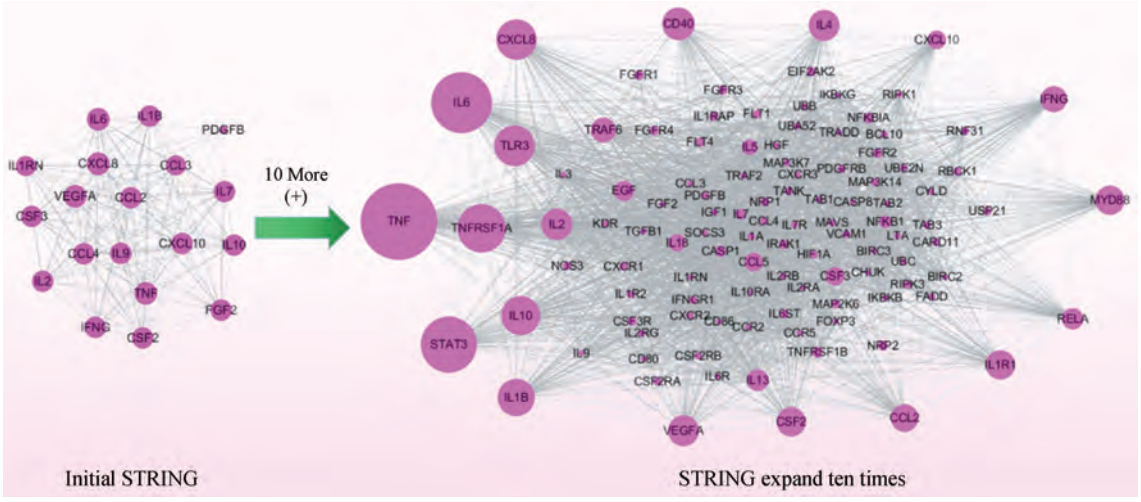

Figure 2 The interaction of 19 cytokines after 10 times of expansion

Figure 3 Distribution and intersection of traditional Chinese medicines acting on cytokines

Table 3　Network topology analysis after 10 times expansion of cytokine targets (Degree ⩾ 70). STAT3: Signal transducer and activator of transcription; TNFRSF1A: Tumor necrosis factor receptor superfamily; TLR3: Toll-like receptors

Official gene symbol	Uniprot ID	Degree
TNF	P01375	97
IL-6	P05231	87
STAT3	P40763	84
TNFRSF1A	P19438	79
CXCL8	P10145	74
TLR3	O15455	74
IL-10	P22301	73
IL-1β	P01584	72

Table 4　Basic information of TCMSP of 22 intersection traditional Chinese medicines

No	TCM	TCMSP monomer	Oral bioavailability (OB) ⩾ 30% Drug-likeness (DL) ⩾ 0.18
1	*Ephedrae Herba*	363	23
2	*Eriobotryae Folium*	304	18
3	*Glycyrrhizae Radix Et Rhizoma*	280	92
4	*Mdri Folium*	269	29
5	*Lonicerae Japonicae Flos*	236	23
6	*Hippophae Fructus*	223	33
7	*Mori Cortex*	194	32
8	*Moslae Herba*	161	15
9	*Schizonepetae Herba*	159	11
10	*Rhododendri Daurici Folium*	154	18
11	*Forsythiae Fructus*	150	23
12	*Tamaricis Cacumen*	121	12
13	*Peucedani Radix*	101	24
14	*Gardeniae Fructus*	98	15
15	*Scutellariae Barbatae Herba*	94	29
16	*Asteris Radix Et Rhizoma*	91	19
17	*Sophorae Tonkinensis Radix Et Rhizoma*	79	21
18	*Polygoni Cuspidati Rhizoma Et Radix*	62	10
19	*Fagopyri Dibotryis Rhizoma*	61	15
20	*Hedysari Radix*	43	14
21	*Mume Fructus*	40	8
22	*Ilicis Chinensis Folium*	38	5

Table 5　Previous experimental studies on the effects of traditional Chinese medicine on cytokines

No.	TCM	Change in related cytokine indicator	Reference
1	*Ephedrae Herba*	IL-4, IL-13, IFNγ, eotaxin ↓	[25, 26]
2	*Glycyrrhizae Radix Et Rhizoma*	TNFα, IL-1β ↓	[27, 28]
3	*Lonicerae Japonicae Flos*	TNFα, IL-1β ↓	[29, 30]
4	*Forsythiae Fructus*	TNFα, IL-6, IL-1β ↓	[31]
5	*Polygoni Cuspidati Rhizoma Et Radix*	TNFα, IL-6, IL-1β, IL-8 ↓	[32, 33]

从中可以发现, 数据库筛选得到的结果不仅与当前《新型冠状病毒感染的肺炎诊疗方案》中推荐的中药种类相吻合, 而且既往的研究也表明这些中药或其有效成分的确可以作用于细胞因子发挥疗效。因此, 借助于细胞因子在TCMSP数据库中筛选的中药可以为临床处方优化及治疗提供参考。

讨论

由上述分析结果可以看出, TNF和IL-6在CS中起着关键的作用, 第七版诊疗方案已经明确将IL-6水平上升作为病情恶化的临床警示指标。大量的研究[34]证实, IL-6激活免疫细胞 (T细胞和巨噬细胞), 清除感染病毒的细胞, 是CS中的主力, 第一级细胞因子称为“初级风暴”, 初级细胞因子可以进一步招募并激活效应细胞及其他细胞, 如$CD8^+$ T细胞、自然杀伤细胞 (natural killer cell, NK)、调节性T细胞 (regulatory cell, Treg) 和辅助型T细胞2 (T helper 2 cell, Th2), 这些细胞还会分泌第二级细胞因子 (次级细胞因子IFNγ和IL-10等), 继续病毒清除过程, 抑制炎症, 并试图恢复肺功能。致命的往往是第二级风暴, 这时细胞因子水平已超出清除病毒所需, 造成过多的炎性细胞聚集。如果大量炎症细胞聚集在肺泡内, 将导致氧合功能下降, 造成呼吸衰竭。基于以上研究分析, 作者认为针对CS治疗应该在病情中期进行, 一旦病情恶化进入第二级风暴阶段将很难医治。

中医药在此次疫情中发挥着重要作用, 第七版诊疗方案中在疾病发展的不同阶段分别给予了不同的中药复方, 从中体现了中医理论中“辨证论治”的重要性, 如: 麻黄出现在进展期的中药处方中, 甘草出现在早、中、重期的处方中等[24]。通过数据库及文献挖掘发现, 多种中药对不同的细胞因子都具有治疗作用, 这也体现了中药多靶点、多层次的作用特点。目前, 国家及各地方的诊疗方案中, 均将中西医结合的方式作为COVID-19临床治疗方案, 尤其是靶向药物在临床上收效良好[35], 这提示某些具有特定功效的中药也可以在针对不同阶段病情处方优化时进行相加减。本文根据“湿毒犯肺”的中医理论和TCMSP数据库筛选出作用于细胞因子风暴的相关中药, 并进一步探讨了5种应用最多的中药的既往研究情况, 以期为防治重症肺炎患者产生的CS进行处方优化以及后续的新药开发提供理论参考。

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