Published By Guangdong Pharmaceutical University, Guangzhou

Journal of Holistic Integrative Pharmacy

2021, 2(1): 26-31

REVIEWS

Research progress of traditional Chinese medicine influencing macrophage polarization

GAO Shuang[1], CHEN Zhe-Sheng[3], CHEN Xuanyu[1], LI Jing[1,2*]

[1]*College of Integrated Traditional Chinese and Western Medicine, Hebei Medical University, Shijiazhuang 050011, China;*

[2]*Department of Traditional Chinese Medicine, Fourth Hospital of Hebei Medical University, Shijiazhuang 050011, China;*

[3]*Department of Pharmaceutical Sciences, College of Pharmacy and Health Sciences, St. John's University, Queens, NY 11439, USA*

[Abstract] Recently, with advancements in science and technology, humans have found that macrophages play essential roles in many diseases, which has become a new focus of research on disease diagnosis and treatment. As traditional Chinese medicine is one of the main tools for disease prevention and treatment, research on its macrophage polarization deserves attention. In this paper, we summarized the effects of traditional Chinese medicine on macrophage polarization in areas such as inhibition of M1 macrophage polarization, inhibition of M2 polarization, and effects on reversal of M1/M2 macrophage phenotype.

[Key words] Traditional Chinese medicine; Macrophages; Polarization; M1 macrophage; M2 macrophage

1 Introduction

Macrophages are widely distributed in the human body and play vital roles in the development and maintenance of homeostasis. As an important component of the innate immune system, macrophages are derived from monocytes, which are differentiated from the monocytic myeloid lineage in the bone marrow. Macrophages have high plasticity and heterogeneity and play key roles in inflammatory responses, tumor immunity, and tissue repair. In response to different environmental stimuli, mature macrophages will polarize into two distinct phenotypes: classically activated macrophages (M1) and alternatively activated macrophages (M2). Macrophages will polarize into M1 macrophages with highly expressed inducible nitric oxide synthase (iNOS), interleukin-12 (IL-12), and CD16/32, under the induction of interferon-γ (INF-γ), lipopolysaccharide (LPS), and tumor necrosis factor-α (TNF-α). INF-γ, LPS, and TNF-α regulate and promote the immune responses of Th1 and Th17 and inhibit tumorigenesis, but may also damage healthy tissues. Alternatively, M2 macrophages are induced and activated by IL-4,

[Research funding]This work was supported by National Natural Science Foundation (81973761) "Study on using Ganrunruyang method to improve Gas6/Ax1 signaling pathway regulated by macrophage polarization in the esophageal cancer microenvironment to inhibit metastasis"; Hebei Provincial Natural Science Foundation (H2019206488) "Mechanistic study on improvement of esophageal cancer cell gap functions to inhibit metastasis by Jiawei Qige San".

[*Corresponding Author] E-mail: lijingtiger@163.com.

These authors have no conflict of interest to declare.

IL-13, IL-10 and highly express argininase-1 (Arg-1), CD206, and IL-10, etc. They have anti-infective effects, promote Th2 immunity, participate in lipid metabolism, allergic reactions, and tumor progression[1-2]. M2 macrophages can be further divided into three subtypes: M2a (induced by IL-4 or IL-13), M2b (induced and activated by LPS and immune complexes), and M2c [induced by glucocorticoids, IL-10, or transforming growth factor (TGF)-β]. According to current studies, many pathways are associated with macrophage polarization, such as *c*-Jun *N*-terminal kinases (JNK), PI3K/Akt, Notch, and JAK/STAT[3]. Recently, some progress has been made on studying the effects of traditional Chinese medicine on macrophage polarization, which has important significance in clinical disease treatment, and are summarized in the following sections.

2 Inhibition of M1 macrophage polarization

2.1 Active ingredients in traditional Chinese medicine

M1 macrophages have pro-inflammatory and antineoplastic effects. The active ingredient of traditional Chinese medicine, curcumin, has anti-infective, antioxidant, anti-fibrosis, and antineoplastic effects[4-5]. It can inhibit the activation of TLR4-MAPK/NF-κB signaling pathway and decrease phosphorylation levels of P38/ERK/JNK/IκBα/P65, thereby inhibiting M1 polarization and decreasing the expression of the inflammatory factors, TNF-α and IL-6[6]. Studies have found that the traditional Chinese medicine, berberine, impacts the energy metabolism of the adipose tissues, decreases the expression of pro-inflammatory factors, and decreases macrophage recruitment, thereby inducing the adipose tissues into M2 macrophage polarization[7]. Loganin, an active ingredient in Cornus officinalis, impacts macrophage polarization, caused by advanced glycosylation end-products (AGEs), by inhibiting M1 macrophage polarization and promotes M2 polarization by mainly acting on the RAGE/RBP-J/IRF8 signaling pathway[8]. Studies showed that polysaccharides of Ganoderma atrum inhibit IL-1β, NO, and ROS synthesis, thereby inhibiting the polarization of M1 macrophages. Additionally, polysaccharides of Anoderma atrum can upregulate MR expression and IL-10 levels in LPS-treated macrophages, thereby promoting the polarization of M2 macrophages[9]. Another study found that pseudolaric acid inhibits LPS-induced inflammatory responses in RAW 264.7 cells and suppresses the macrophage bias toward the M1 phenotype, which is associated with the impact of cell cycle distribution regulation of the F-κB/PPARγ pathway[10]. As an active ingredient of ginseng, ginsenoside Rd (GSRd) regulates M1 macrophage polarization to reduce macrophage infiltration and secretion of inflammatory cytokines. Therefore, GSRd plays a protective role in renal ischemia-reperfusion injuries[11]. Salidroside (SLDS) obtained from the root extract of Rhodiola rosea, affects decreases in the polarization of cortical and striatal M1 macrophage/microglial cells in mice with middle cerebral artery occlusion and increases in the polarization of M2 macrophage/microglial cells. These results provide evidence that SLDS drives M2 polarization[12]. The above experiments showed that traditional Chinese medicine's active ingredients could regulate related protein pathways or cytokines, impacting macrophage polarization.

2.2 Traditional Chinese medicine compound

Sinisan, which is composed of *Bupleurum chinense*, *Paeonia sterniana*, *Aurantii fructus immaturus*, and *Glycyrrhiza uralensis*, has anti-infective effects. LPS-stimulated RAW264 cells were used as an in vitro model and treated with different mass concentrations of Sinisan. It was found that Sinisan can inhibit LPS-induced proliferation, decrease the stimulatory effects of LPS, decrease the

release of M1 polarization-related cytokines (TNF-α, IL-6, and IL-1β) and mRNA levels of TNF-α and IL-6, and increase the release of M2 polarization-related cytokine IL-10 and mRNA levels of IL-10 and Arg-1[13]. Tian[14] proved that a specific dose of serum containing Huanglian detoxification decoction can promote the differentiation of Mφ to M2, promote the secretion of anti-inflammatory TGF-α, and limit the differentiation of pro-inflammatory M1 macrophages. He et al.[15] found that Ermiaosan can inhibit M1 polarization of LPS+ IFN-γ-induced macrophages but cannot inhibit M2 polarization of IL-4+ IL-13-induced macrophages. Li[16] found that different concentrations of serum containing PSORI-CM02 (Paeonia anomala, Sarcandra glabra, Smilax glabra, and Curcuma zedoaria) can inhibit the growth of peritoneal macrophages in M1 mice. Zhou et al.[17] found that the traditional Chinese medicine compound, Shenglian extract, can inhibit the expression of cell membrane molecules in M1 macrophages, decrease secretion and levels of inflammatory factors, and inhibit M1 polarization of macrophages. Moreover, all concentrations demonstrate effects without concentration-dependence. The above studies proved that traditional Chinese medicine compounds inhibit the expression of relevant cytokines by impacting on different pathways, consequently affecting macrophage polarization. Moreover, different pharmaceutical ingredients in compound preparation or drug concentration will affect the macrophage polarization phenotype.

2.3 Acupuncture and other methods involving traditional Chinese medicine

Morgana et al.[18] conducted a study on mice and found that manual acupuncture on the "Sanyinjiao" (SP6) acupoint can alleviate pain behavior, mechanical hyperalgesia, edema, and heat production. Acupuncture SP6 increased IL-10 levels but did not affect the pain behavior and edema in IL-10-knockout mice. Repeated acupuncture can induce the phenotype conversion of muscle macrophages, decrease pro-inflammatory M1 macrophages, and increase anti-infective M2 macrophages. Li et al.[19] found that the "Zusanli" (ST36) and "Feishu" (BL13) electroacupuncture can decrease inflammatory responses in rats with chronic obstructive pulmonary disease. This method may inhibit the MyD88/NF-κB p65 signaling pathway via electroacupuncture, thereby inhibiting the polarization of M1 macrophages. The above studies showed that manual acupuncture and electroacupuncture could act on macrophage polarization to regulate and control the occurrence and progression of inflammation and thereby treat related diseases.

3 Inhibition of M2 macrophage polarization

M2 macrophage polarization is associated with allergic reactions, progression, and tumor metastases. Inhibition of M2 macrophage polarization has become an important research area in certain anaphylactic diseases and tumor treatments. Zheng et al.[20] found that icariin can decrease the infiltration of M2 macrophages in pancreatic cancer and the quantity of splenic M2 macrophages. Guben Fangxiao decoction, derived from Yuping Fengsan and Erchen Tang, can improve the equilibrium of Th1/Th2, inhibit alternative activation of macrophages, and polarize M2 macrophages[21]. From studies on idiopathic pulmonary fibrosis (IPF), the traditional Chinese medicine, Schisandra chinensis, can inhibit the progression of IPF and M2 macrophage polarization via the TGF-β1/Smad signaling pathway[22]. Jia et al.[23] found that Fuzheng Jiedu Fang can decrease the infiltration of CD68+ macrophages, decrease levels of M2 macrophages, and inhibit levels of inflammatory factors, thereby inhibiting gastric cancer in mice. The above studies found that traditional Chinese medicine could inhibit M2 macrophage polarization through cytokines and signaling pathways to prevent and control some diseases.

4 Reversal of M1/M2 macrophage phenotype

Many active ingredients of traditional Chinese medicine can promote the reversal of the M1/M2 phenotype. A study[24] found that polysaccharides of *Polyporus umbellatus* significantly increase the positive expression of CD16/32 and CD40 as well as the expression level of inflammatory cytokines, which proved that polysaccharides of *Polyporus umbellatus* could reverse M2 macrophages to pro-inflammatory M1 macrophages, thereby improving the immune effects of macrophages. Zhang et al.[25] proved that icariin could significantly induce M2 macrophage polarization and promote the expression of M2 macrophage marker genes (IL-10 and Arg) with significant periodicity in terms of time and induce dose-dependent transformation of differentiated M1 macrophages to M2 macrophages. Further, LPS can promote the M1 polarization of RAW264.7 cells. A study reported that Dendrobium officinale polysaccharide could reverse the effects of LPS, thereby promoting M2 polarization of RAW264.7 cells and the secretion of anti-inflammatory factors [26].

Also, traditional Chinese medicine compounds have related effects. Qishen granules made from traditional Chinese medicine preparations, Zhenwu and Simiao Yongan decoction, could restore M1/M2 macrophage imbalance in cardiomyocytes to alleviate myocardial fibrosis and inhibit the TGF-β1/Smad3 pathway that activates macrophages and promotes M2 macrophage-dependent angiogenesis. Restoring the equilibrium of M1/M2 macrophages may be an effective strategy for improving myocardial remodeling[27]. Tian[28] found that Buyang Huanwu decoction can significantly inhibit the expression of iNOS, TNF-α, CD16/32 while promoting the expression of Arg-1, IL-10, and CD206, which proved that it could promote the conversion of M1 to M2 macrophages in tissues of spinal cord and spleen when there is experimental autoimmune encephalomyelitis. Li [29] proved that Yangyin Hewei Fang could decrease M1 macrophage levels and increase M2 macrophage levels in gastric tissues of rats with diabetic gastroparesis, thereby improving gastric motility. Simultaneously, studies showed that moxibustion could upregulate CD163 macrophage and the expression level of key cytokines, IL-4 and IL-13, related to differentiation in lung tissue of rats with ulcerative colitis and downregulate CD86 and differentiation-related cytokines, IFN-γ and TNF-α, to promote the conversion of M1 to M2 macrophages[30]. The above studies proved that traditional Chinese medicine could promote the reversal of M1/M2 macrophage phenotype and regulate the equilibrium of M1/M2. Certain traditional Chinese medicines have bidirectional regulatory roles, which have important significance in treating related diseases.

5 Conclusion and prospects

In traditional Chinese medicines, macrophages have become an important research area in disease treatment. Traditional Chinese medicines can regulate certain signaling pathways and change the microenvironment of macrophages to impact macrophage polarization. Traditional Chinese medicines have bidirectional regulatory effects on macrophage polarization, where some have shown temporal periodicity and dose-dependence. However, there are still some study concerns regarding the effects of macrophage polarization, including that most studies focused on a single traditional Chinese medicine and its active ingredients. Therefore, comprehensive studies on traditional Chinese medicine compound preparations are required. This study primarily focused on a few diseases and needs further expansion. These concerns need to be individually resolved in future studies.

Traditional Chinese medicine is an integral component of modern medicine, which has extremely high potential in terms of development and has important effects in preventing and treating many diseases. We believe that continuous in-depth

research on its effects on macrophage polarization will enable traditional Chinese medicine to demonstrate its strengths and be widely used in treating and controlling clinical diseases.

References

[1] Funes SC, Rios M, Escobar-Vera J, et al. Implications of macrophage polarization in autoimmunity[J]. *Immunology,* 2018, 154(2):186-195.

[2] Kratochvill F, Neale G, Haverkamp JM, et al. TNF counterbalances the emergence of M2 tumor macrophages[J]. *Cell Rep,* 2015, 12(11):1902-1914.

[3] Zhou D, Huang C, Lin Z, et al. Macrophage polarization and function with emphasis on the evolving roles of coordinated regulation of cellular signaling pathways[J]. *Cell Signal,* 2014, 26(2):192-197.

[4] Song LP, Wang Y. Research progress of pharmacological effect and mechanism of curcumin[J]. *China Medical Herald,* 2020, 17(20):29-33 (in Chinese).

[5] Bordoloi D, Roy NK, Monisha J, et al. Multi-targeted agents in cancer cell chemosensitization: what we learnt from curcumin thus far[J]. *Recent Pat Anticancer Drug Discov,* 2016, 11(1):67-97.

[6] Tang B, Zhou YY. Effects of curcumin on macrophage polarization and inflammatory responses via the TLR4-MAPK/NF-κB signaling pathway[J]. *J Electrocardiol Circ,* 2019, 38(5):389-394 (in Chinese).

[7] Lin J, Cai Q, Liang B, et al. Berberine, a traditional Chinese medicine, reduces inflammation in adipose tissue, polarizes M2 macrophages, and increases energy expenditure in mice fed a high-fat diet[J]. *Med Sci Monit,* 2019, 25:87-97.

[8] Gan XY, Wang W, Lu Y, et al. Effects of Loganin on macrophage polarization induced by AGEs[J]. *J Nanjing Univ Tradit Chin Med,* 2020, 36(1):46-50 (in Chinese).

[9] Liu X, Fu WW, Niu XQ, et al. Effects of Ganoderma atrum polysaccharide on M1/M2 phenotype conversion in lipopolysaccharide-induced macrophages[J]. *Food Sci Hum Well,* 2018, 39(19):141-146 (in Chinese).

[10] Li YX, Li Q, Ji WJ, et al. Inhibitory effects of pseudolaric acid B on inflammatory response and M1 phenotype polarization in RAW264.7 macrophages induced by lipopolysaccharide[J]. *Chinese J Cellular Mol Immunol,* 2016, 32(5):625-629 (in Chinese).

[11] Ren K, Jin C, Ma P, et al.Ginsenoside Rd alleviates mouse acute renal ischemia/reperfusion injury by modulating macrophage phenotype[J]. *J Ginseng Res,* 2016, 40(2):196-202.

[12] Liu X, Wen S, Yan F, et al. Salidroside provides neuroprotection by modulating microglial polarization after cerebral ischemia[J]. *J Neuroinflammation,* 2018, 15(1):39.

[13] Fan HJ, Tan ZB, Liang HF. Effects of Sinisan on macrophage polarization of lipopolysaccharide-induced RAW264.7 cells[J]. *Chin J Exp Tradit Med Formulae,* 2019, 25(13):9-14 (in Chinese).

[14] Tian WY. Examining the effects and mechanisms of Huanglian detoxification soup in AS intervention based on M1/M2 Mφ polarization and inflammation regulating effects[D]. Changsha: Hunan University of Chinese Medicine, 2015 (in Chinese).

[15] He LH, Qin QX, Wang H. Effects of Ermiao San on M1/M2 polarization of rat bone marrow-derived macrophages[J]. *Chin J Exp Tradit Med Formulae,* 2020, 26(11):71-77 (in Chinese).

[16] Li L. Therapeutic effects and macrophage polarization effects of PSORI-CMO2 in a mouse model of psoriasis[D]. Guangzhou: Guangzhou University of Chinese Medicine, 2017 (in Chinese).

[17] Zhou BB, Li YJ, Li Q, et al. Effects of Shenglian extract on M1 macrophages[J]. *China J Chin Mater Med,* 2014, 39(11):2086-2090 (in Chinese).

[18] Da S M, Bobinski F, Sato K L, et al. IL-10 cytokine released from M2 macrophages is crucial for analgesic and anti-inflammatory effects of acupuncture in a model of inflammatory muscle pain[J]. *Mol Neurobiol,* 2015, 51(1):19-31.

[19] Li Y, Zhang XF, Liu ZB, et al. Effects of electroacupuncture on M1 polarization of alveolar macrophages in rats with chronic obstructive pulmonary disease[J]. *Acupunc Res,* 2020, 45(3):173-179 (in Chinese).

[20] Zheng X, Li D, Li J, et al. Optimization of the process for purifying icariin from Herba Epimedii by macroporous resin and the regulatory role of icariin in the tumor immune microenvironment[J]. *Biomed Pharmacother,* 2019, 118:109275.

[21] Liu LW, Xing QQ, Zhao X, et al. Proteomic analysis provides insights into the therapeutic effect of GU-BEN-FANG-XIAO decoction on a persistent asthmatic mouse model[J]. *Front Pharmacol,* 2019, 10:441.

[22] Guo Z, Li S, Zhang N, et al. Schisandra inhibit bleomycin-induced idiopathic pulmonary fibrosis in rats via suppressing M2 macrophage polarization[J]. *Biomed Res Int,* 2020, 2020:5137349.

[23] Jia CH, Li FF, He LS, et al. Intervention study on Fuzheng Jiedu Fang on macrophages and related cytokines in a model of postoperative relapse in anterior stomach tumor-bearing mice[J]. *Chin J Basic Med Tradit Chin Med,* 2014, 20(6):748-751 (in Chinese).

[24] Jiang ZB, Zhao J, Li SM, et al. Conversion of M2 macrophages to M1 macrophages induced by polyporus polysaccharide[J]. *Chin J Immunol,* 2015, 31(8):1049-1052 (in Chinese).

[25] Zhang WP, Liu CY, Zhou J. Effects of icariin on M1/M2 conversion in lipopolysaccharide-induced RAW264.7 cells[J]. *China J Tradit Chin Med and Pharm,* 2016, 31(10):4239-4242 (in Chinese).

[26] Huang J, Zhang Y, Yan Q. Immunoregulatory effects of Dendrobium officinale polysaccharide on lipopolysaccharide-induced macrophages[J]. *Chin Pharm J*, 2017, 52(7):548-552 (in Chinese).

[27] Lu W, Wang Q, Sun X, et al. Qishen granule improved cardiac remodeling via balancing M1 and M2 macrophages[J]. *Front Pharmacol*, 2019, 10:1399.

[28] Tian QQ. Immunoregulatory effect of Buyang Huanwu Decoction on Mononuclear Macrophages in mice with experimental autoimmune encephalomyelitis[D]. Taiyuan: Shanxi University of Traditional Chinese Medicine, 2017 (in Chinese).

[29] Li YQ. Effect of YangyinHewei Formula on M1/M2 dynamic balance and HO-1 in rats model of Diabetic Gastroparesis[D]. Nanjing: Nanjing University of Chinese Medicine, 2019 (in Chinese).

[30] Zhong R, Zhou ZG, Zhou MR, et al. Research progress on the adaptive immune mechanisms of moxibustion in the treatment of ulcerative colitis[J]. *Jiangxi J Tradit Chin Med*, 2020, 51(2):68-72 (in Chinese).