Research Progress on the Role of Mitophagy in Macrophage Polarization in Sepsis Immunomodulation and Traditional Chinese Medicine Intervention

Authors: Qi Luyao, Xing Jixiang, Ouyang Bingqing, Li Yunfeng, Lei Ming, Thunder

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Abstract

Sepsis is an organ dysfunction syndrome caused by infection, characterized by high incidence and mortality rates, complex pathogenesis that can trigger cascading immune responses, and currently lacks specific therapeutic agents. Currently, sepsis treatment primarily employs Western supportive therapies such as antibiotics, hemodynamic management, and mechanical ventilation; however, as immune cascade reactions emerge, patients' susceptibility to secondary infections increases significantly, predisposing them to septic shock and resulting in poor prognosis. International consensus proposes that initiating dynamic monitoring of patients' immune function within 48 hours of sepsis diagnosis can effectively slow disease progression. Numerous studies have demonstrated that macrophages, as the first line of defense in the innate immune system against pathogens, play a crucial role in treating various immune system diseases by regulating polarization and the activation ratio of cytokines. Meanwhile, mitochondrial autophagy has emerged as a research hotspot in recent years, with mounting evidence indicating its pivotal role in regulating inflammatory signal transduction. On one hand, during the inflammatory storm phase, promoting mitochondrial autophagy can mitigate uncontrolled infection and excessive inflammation in sepsis; on the other hand, during the immunosuppressive phase, inhibiting mitochondrial autophagy can enhance systemic immunity, promote bacterial clearance, and improve patient survival rates. Notably, Traditional Chinese Medicine (TCM) embodies the philosophy of 'treating pre-disease,' which aligns seamlessly with the 'prevention and interception' concept in current sepsis expert consensus. TCM therapeutic modalities, including herbal monomers, compound formulas, and acupuncture, employ treatment principles of clearing heat and detoxifying, activating blood circulation and resolving sta-

sis, strengthening the body and consolidating the root, and purging the interior to bidirectionally regulate levels of mitochondrial autophagy-related proteins such as PINK1, Parkin, LC3, and P62, dynamically balance the M1/M2 macrophage ratio, and achieve effects of preventing, reversing, or even intercepting sepsis progression, thereby providing a novel approach of 'preventing disease before onset and preventing deterioration after disease onset' for sepsis.

Full Text

Role of Mitophagy Affecting Macrophage Polarization in Sepsis Immunomodulation and Research Progress on Traditional Chinese Medicine Intervention

Qi Luyao[1], Xing Jixiang[2], Ouyang Bingqing[1], Li Yunfeng[1], Lei Ming[1]*

[1]Department of Critical Care Medicine, The Seventh People's Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai 200137, China
[2]Graduate School, Tianjin University of Traditional Chinese Medicine, Tianjin 301617, China

Abstract

Sepsis is an organ dysfunction syndrome caused by infection, characterized by high morbidity and mortality, complex pathogenesis, and the ability to trigger cascading immune responses, with no specific cure currently available. Presently, sepsis treatment primarily employs Western supportive therapies including antibiotics, hemodynamic management, and mechanical ventilation. However, as immune chain reactions emerge, patients' susceptibility to secondary infections increases significantly, often progressing to septic shock with poor prognosis. International consensus recommends initiating dynamic monitoring of immune function within 48 hours of sepsis diagnosis to effectively slow disease progression. Numerous studies have identified macrophages, as the first line of defense in innate immunity against pathogens, as playing crucial roles in treating various immune system diseases by regulating polarization and cytokine activation ratios. Mitophagy, a research hotspot in recent years, has increasingly been shown to play a key role in regulating inflammatory signal transduction. On one hand, promoting mitophagy during the inflammatory storm phase can alleviate uncontrolled infection and excessive inflammation in sepsis; on the other hand, inhibiting mitophagy during the immunosuppressive phase can enhance immunity, promote bacterial clearance, and improve survival rates. Notably, Traditional Chinese Medicine (TCM), with its "treating before illness" philosophy, aligns with the "prevention and interruption" concept in current sepsis expert consensus. TCM interventions—including herbal monomers, compound formulas, and acupuncture—employ therapeutic principles of clearing heat and removing toxins, activating blood circulation and resolving stasis, strengthening vital qi and consolidating the root, and purging the interior to bidirectionally

regulate mitophagy-related proteins such as PINK1, Parkin, LC3, and P62, while dynamically balancing M1/M2 macrophage ratios. This achieves effects of preventing, reversing, or even interrupting sepsis progression, offering a novel approach of "preventing disease before onset and preventing progression after onset" for sepsis management.

Keywords: sepsis; mitophagy; macrophage polarization; immune regulation; Traditional Chinese Medicine

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Sepsis is a syndrome of life-threatening organ dysfunction caused by a dysregulated host response to infection. Its pathogenesis is extremely complex, encompassing pathophysiological processes such as inflammatory imbalance, immune dysfunction, mitochondrial damage, coagulation disorders, neuroendocrine transmission abnormalities, and autophagy, involving functional changes in multiple organs [1]. During this period, the body triggers complex immune responses, transitioning from hyperinflammatory cytokine storms to later-stage immunosuppression and immune deficiency [2]. If not properly managed, this readily leads to circulatory and cellular metabolic disorders, progression to septic shock, and significantly increased mortality [3]. According to the latest global statistics, sepsis accounts for approximately 19.7% of all deaths worldwide [4]. In China, the annual standardized incidence of sepsis hospitalizations shows a year-by-year increasing trend, further increasing national and financial burdens [5]. The latest "Expert Consensus on Sepsis Immune Monitoring and Treatment" recommends initiating dynamic monitoring of immune function within 48 hours of sepsis diagnosis to early identify immune dysfunction, enabling early assessment and management of immune status to effectively slow sepsis progression and improve patient prognosis [6]. Consequently, recent sepsis research has increasingly focused on regulating immune dysfunction [7]. However, Western medicine lacks effective solutions for sepsis-induced immune dysfunction, with guidelines offering only weak recommendations or no recommendation for thymalfasin and immunoglobulin [6]. As a traditional medicine of China, TCM's "treating before illness" theoretical foundation aligns with the "prevention and interruption" concept in China's current sepsis expert consensus [8]. Therefore, exploring effective TCM interventions to early regulate immune function in sepsis patients, effectively blocking immunosuppression before it occurs, represents an urgent global public health challenge.

1. Overview of Mitophagy and Macrophage Polarization

1.1 Overview of Mitophagy

Mitochondria are the primary site of aerobic respiration in living cells. Normal mitochondrial function is fundamental to maintaining metabolic energy supply and is indispensable for immune signal transduction, with mitophagy homeostasis being the cornerstone of normal mitochondrial function [9]. Mitophagy

refers to a selective autophagy process induced by external stimuli such as reactive oxygen species (ROS), nutrient deficiency, and cellular senescence [10], which induces membrane segregation, enclosure, and lysosomal degradation of organelles. It eliminates damaged or excess mitochondria, promotes balance in mitochondrial quantity and quality, and represents a crucial component of mitochondrial quality control. Mitophagy is closely associated with the development of various diseases including neurodegenerative disorders, cancer, and cardiovascular diseases [11]. Literature confirms that mitophagy is a "double-edged sword" with complex mechanisms where benefits and risks coexist, and future efforts should focus on maximizing its benefits [12]. BCL2/adenovirus E1B 19kDa protein-interacting protein 3 (BNIP3/NIX) and FUN14 domain-containing protein 1 (FUNDC1) are the two primary receptor groups mediating mitophagy under physiological and pathological conditions in mammals. The PTEN-induced kinase 1 (PINK1)/E3 ubiquitin ligase Parkin pathway is currently the most recognized pathway supporting mitophagy-mediated autophagosome formation, autophagy adaptor recruitment, and TANK-binding kinase 1 (TBK1)-driven autophagy receptor phosphorylation [13] (see Figure 1 [Figure 1: see original paper]).

1.2 Overview of Macrophage Polarization

Macrophages serve as the first line of defense in innate immunity against pathogen exposure. Through phagocytosis, they perform critical host defense mechanisms, recruit other immune cells to infection sites, activate the serum complement system and adaptive immune responses, and phagocytose and eliminate foreign pathogens, thereby exerting immunomodulatory effects [14-15]. Some perspectives suggest that polarized macrophages primarily manifest as classically activated macrophages mediating pro-inflammatory responses (M1 type, mainly induced by lipopolysaccharide [LPS], secreting tumor necrosis factor-α [TNF-α], interleukin [IL]-1β, IL-6, IL-8, IL-12, with cluster of differentiation [CD]80, CD86, and inducible nitric oxide synthase [iNOS] as primary surface markers, causing inflammatory responses and pathogen phagocytosis and killing) and alternatively activated macrophages mediating anti-inflammatory responses (M2 type, mainly induced by IL-4, secreting IL-10, transforming growth factor-β [TGF-β], vascular endothelial growth factor [VEGF], with CD206, CD163, and arginase 1 [Arg-1] as primary surface markers, reducing inflammation and promoting tissue repair and regeneration) [16] (see Figure 2 [Figure 2: see original paper]). Additional studies show macrophages can be broadly divided into three functional groups: host defense macrophages (similar to M1), wound-healing macrophages (similar to M2), and immunoregulatory macrophages (mediated by factors secreted by Treg cells, memory CD4+ T cells, etc., primarily exhibiting immunomodulation, immune tolerance, and immunosuppression). The same macrophage may possess characteristics of two populations, and different functional groups can transform into each other. Macrophage polarization state transitions play important roles in immune responses to various diseases including pathogen

infection, tumors, and autoimmune diseases [17]. Currently, personalized macrophage-targeting strategies are extensively studied in disease treatment [18].

2. Role of Mitophagy Regulating Macrophage Polarization in Sepsis

2.1 Role of Macrophage Polarization in Sepsis

Macrophages, as sentinel cells of innate immunity, originate from hematopoietic stem cells and transform from monocytes entering damaged tissues. They distribute through peripheral blood to various target organs including liver, heart, lungs, spleen, kidneys, brain, skin, and vascular endothelium, primarily governing the release of multiple inflammatory cytokines such as IL-1β, IL-6, IL-8, IL-12, IL-18, IL-33, TNF-α, granulocyte-macrophage colony-stimulating factor (GM-CSF), macrophage migration inhibitory factor (MIF), monocyte chemoattractant protein (MCP)-1, IL-1ra, TGF-β, and prostaglandin E2, as well as active substances including interferons and complement [19]. Their activation dysregulation directly affects sepsis outcomes [20-21].

In early-stage sepsis, pro-inflammatory factors such as interferon-γ (IFN-γ) and LPS induce macrophage polarization toward the M1 phenotype. Persistent M1 macrophage increase releases massive inflammatory factors including IL-1, TNF-α, IL-6, ROS, and iNOS, causing severe systemic inflammatory cytokine storms that damage target organs and create cascading organ dysfunction [22]. Studies find that when sepsis macrophages are stimulated, matrix metalloproteinase-9 (MMP-9) levels are highly expressed, positively correlating with disease severity [23]. Macrophage-produced TNF-α and IL-1β can activate neutrophils during sepsis, where polymorphonuclear neutrophils secrete exosomal miR-30d-5p, inducing pyroptosis through activation of the nuclear factor- B (NF- B) signaling pathway, causing pathological tissue changes and promoting sepsis-related acute lung injury (ALI) [24]. Toll-like receptor 4 (TLR4) regulates macrophage polarization from M1 to M2 subtypes by mediating NF- B and mitogen-activated protein kinase (MAPK) signal transduction, maintaining mitochondrial dynamics balance in tissues, reducing oxidative stress and apoptosis, and alleviating sepsis-induced myocardial injury [25]. Targeted macrophage delivery of miR-21 for reprogramming (reducing M1, activating M2), focusing on inflammatory regulation of macrophage phenotypes, can reverse myocardial remodeling and prevent vascular ischemia-reperfusion injury [26]. Krüppel-like transcription factor (KLF) 14 can significantly reduce inflammatory levels in mice and improve survival rates in sepsis by regulating macrophage glycolysis through inhibition of hexokinase 2 (HK2) [27].

Conversely, in late-stage sepsis, M1 macrophage secretion is blocked while M2 macrophage secretion becomes excessive, or both M1 and M2 macrophage secretions are suppressed, inducing host immunosuppression. At this stage, susceptibility to opportunistic and nosocomial secondary infections increases signifi-

cantly [28]. The "gold standard" sepsis model using cecal ligation and puncture (CLP) shows the transition point from hyperinflammation to immunosuppression occurs on the first day after CLP surgery (within 24 hours) [29-30]. Clinical observations reveal that compared with children without immune paralysis, pediatric sepsis patients with immune paralysis exhibit lower mitochondrial respiration in peripheral blood mononuclear cells (PBMCs), with immune paralysis and low mitochondrial respiration subpopulations showing the highest levels of systemic inflammation [31]. In a double-blind, randomized controlled clinical study of 240 sepsis patients caused by pulmonary infection, bacteremia, or acute cholangitis, measuring serum ferritin and human leukocyte DR antigen (HLA-DR)/CD14, immune paralysis patients showed higher mortality rates compared with non-immune paralysis patients [32].

2.2 Role of Mitophagy in Regulating Macrophage Polarization

As the primary energy provider for macrophage polarization, mitochondria produce adenosine triphosphate (ATP) required for cellular metabolism when functioning normally. When damaged, they generate ROS and initiate mitophagy. Mitophagy is inherently a self-protective mechanism through which cells clear damaged mitochondria, prevent protein accumulation, inhibit ROS generation, and maintain mitochondrial quantity and quality homeostasis to preserve normal physiological function [33]. However, excessive mitophagy leads to excessive mitochondrial elimination, causing mitochondrial deficiency and behavioral disorders such as anxiety-like and depression-like behaviors [34]. Numerous studies have investigated mitophagy's role in regulating macrophage polarization mechanisms [35-36]. Increasing evidence indicates mitophagy plays a key role in regulating inflammatory signal transduction and shows promise as a therapeutic target for innate immunity in sepsis infection [37].

Studies demonstrate that endosomal adaptor protein APPL1 deficiency inhibits mitophagy, leading to accumulation of damaged mitochondria that produce ROS and oxidized mitochondrial DNA (mtDNA), triggering excessive activation of NOD-like receptor thermal protein domain associated protein 3 (NLRP3) inflammasomes in macrophages. This enhances systemic cysteine-aspartic acid protease (caspase)-1 activation and increases IL-1β production and secretion, representing an important mechanism for endotoxin-induced sepsis inflammatory cytokine storms [35]. In LPS-induced sepsis mice, specific overexpression of the autophagy key regulatory protein complex Beclin-1 can alleviate uncontrolled infection and excessive inflammation induced by M1 macrophage polarization by inhibiting release of mitochondrial danger-associated molecular patterns (DAMPs) and activating the PINK1/Parkin pathway to promote mitophagy, improving cardiac fibrosis and heart function in sepsis mice. Inhibiting mitophagy produces opposite effects [38-39]. Ubiquitin-specific protease 19 (USP19) can inhibit NLRP3 inflammasome activation by increasing autophagic flux and reducing mitochondrial ROS production, thereby promoting M2-like macrophage polarization and representing a potential therapeutic target for in-

flammatory intervention [40].

Conversely, other studies indicate that inhibiting mitophagy is a physiological mechanism that helps activate myeloid cells and improve sepsis prognosis. Using bone marrow with Pink1 deficiency or pharmacological inhibition of mitophagy promotes macrophage activation, facilitating bacterial clearance and improving survival rates. Conversely, using mitochondrial uncouplers that promote mitophagy reverses LPS/IFN-γ-mediated macrophage activation, leading to immune paralysis, impaired bacterial clearance, and reduced survival rates [36].

These findings reveal controversies in Western medicine regarding how to regulate the relationship between mitophagy and macrophage polarization to achieve sepsis recovery and the optimal timing for intervention. Moreover, a dynamic bidirectional regulatory chain reaction likely exists between these two factors. Consequently, TCM's "treating before illness" philosophy and "bidirectional regulation" mechanisms become particularly prominent.

3. Application of Traditional Chinese Medicine Regulating Mitophagy to Affect Macrophage Polarization in Sepsis Immunomodulation

Traditional Chinese medical texts do not describe sepsis as a specific disease entity, but its symptoms can be categorized under "external febrile diseases," "cold damage," or "warm diseases." Low immunity in sepsis is typically associated with spleen qi deficiency, spleen-stomach dysfunction preventing distribution of nutrients, combined with congenital deficiency and qi-blood imbalance—"where evil accumulates, qi must be deficient." Modern physicians consider "toxin," "stasis," and "deficiency" as the trilogy of sepsis progression, with vital qi deficiency persisting throughout the disease course. TCM can exert four major functions—"prevention, control, treatment, and recovery"—at different disease stages [41-42]. Herbal medicine and acupuncture often "reduce excess and supplement deficiency," providing bidirectional regulation during disease progression [43], both clearing heat and resolving toxins to correct inflammatory reactions [44] and supplementing vital qi to alleviate immunosuppression [45].

3.1 Chinese Medicine Monomers

With deepening TCM research innovation, separation and extraction technologies have advanced considerably, enabling preparation and analysis of effective, non-toxic, consistent, and stable Chinese medicine monomer components, attracting increasing attention [46].

Paeoniflorin (PF), a water-soluble monoterpene glycoside extracted from Paeonia, can repair damaged mitochondria by increasing mitochondrial membrane potential (MMP) and reducing ROS accumulation. Simultaneously, it upreg-

ulates mitophagy-related proteins PINK1, Parkin, BNIP3, and P62, increases KLF4 expression, inhibits infiltration of M1 macrophage markers CD68 and iNOS in kidney tissue, reduces pro-inflammatory factors including IL-6, IL-1β, TNF-α, and MCP-1, increases the proportion of M2 macrophage marker CD206, and elevates anti-inflammatory markers including Arg1, resistin-like molecule α (Fizz1), IL-10, and Ym-1. This promotes macrophage polarization from M1 to M2 phenotype, protecting capsular cells and kidney tissue from inflammatory damage in experimental mice, demonstrating concentration- and function-dependent bidirectional immunomodulation [44]. Chan et al. found that triptolide from Tripterygium wilfordii may increase cellular ROS production and activate caspase family expression and programmed cell death (particularly apoptosis) through autophagy-apoptosis cross-talk, increased acidic vacuoles, LC-3 expression, and elevated ATG-like protein levels, stimulating autophagy in LPS-pretreated cells. Concurrently, it can increase MMP, significantly enhance cell populations of T cells, B cells, monocytes, and macrophages, and augment phagocytosis of peripheral blood mononuclear cell macrophages (PBMCs), exerting anti-inflammatory, anti-proliferative, pro-apoptotic, and immune-enhancing effects [47].

Quercetin (Qu), a natural polyphenolic flavonoid with anti-inflammatory and antioxidant properties, can prevent neuronal damage by promoting mitophagy to inhibit mtROS-mediated NLRP3 inflammasome activation in microglia [48]. Similarly, baicalin can significantly downregulate light chain 3 (LC3) II/I, P62, and translocase of outer mitochondrial membrane 20 (TOM20) levels while upregulating NIX, adenosine monophosphate-activated protein kinase (AMPK), and peroxisome proliferator-activated receptor-γ coactivator (PGC)-1α levels, improving mitophagy status in hippocampal neurons and thereby alleviating mitochondrial structural and functional damage to ameliorate depression-like behaviors in mice [49]. Ginseng root extract strongly induces autophagy through the Akt-mTOR signaling pathway, alleviating excessive oxidation, mitochondrial dysfunction, and inflammation. It enhances Beclin-1, LC3 II, and Atg7 protein expression, markedly reduces nitric oxide, TNF-α, and IL-6 secretion in LPS-treated cells, upregulates IL-10 mRNA levels, downregulates IL-6 and IL-1β mRNA levels, alleviates dextran sulfate sodium (DSS)-induced colitis damage, and exerts effects similar to NF- B and amino-terminal kinase (JNK) inhibitors [50].

Puerarin provides bidirectional regulation of mitophagy. On one hand, it can alleviate LPS-induced mitochondrial damage in H9C2 cells by regulating dynamin-related protein 1 (Drp1) and mitofusin 1 (MFN1), reverse LPS-induced reductions in mitochondrial enzyme activity, adenosine monophosphate (AMP), adenosine diphosphate (ADP), and ATP levels, and mediate p62, LC3B, Pink1, and Parkin to promote mitophagy in H9C2 cells, preventing adverse cardiovascular effects in sepsis [51]. On the other hand, it can upregulate phosphoinositide-3-kinase (PI3K), protein kinase B (Akt), and mammalian target of rapamycin (mTOR) phosphorylation levels, activate the PI3K/Akt/mTOR signaling pathway, reverse MMP and ATP content, inhibit FUNDC1-mediated mitophagy and

apoptosis in human bronchial epithelial cells, and protect against excessive oxidative damage, similar to the effect of mitochondrial division inhibitor (Mdivi) in suppressing autophagy-related protein expression [52].

Euphorbia kansui is clinically used to treat bacterial and viral infections, cancer, leukemia, convulsions, and other diseases [53], with its main active monomer being C21 steroidal glycosides. C21 steroidal glycosides can induce typical apoptotic characteristics in HepG2 cells (a human hepatoma cell line), such as morphological changes and caspase cascade reactions. The mechanism involves inducing mitochondrial dysfunction and ROS accumulation to initiate mitophagy-dependent apoptosis, promoting degradation of the sodium-potassium pump ATPase $ 1subunit(ATP1A1), inhibitingtheATP1A1 - AKT/ERKsignalingpathway, andregulatingreleaseofinflammatorycytokinesincludingTNF- $ and IFN-γ, thereby regulating M2 subtype macrophage polarization, promoting macrophage phagocytosis, enhancing immunity, and eliminating pathogens [54].

Cryptotanshinone (CPT), the main lipophilic extract of Salvia miltiorrhiza belonging to diterpenoid quinone compounds, exhibits anti-tumor, antioxidant, anti-inflammatory, and antibacterial activities [55]. As an anti-tumor immunomodulator, it can inhibit mitochondrial oxidative phosphorylation and mitochondrial fusion through apoptosis signal-regulating kinase 1 (ASK1) pathway-mediated autophagy and transcriptional activation, suppress mitophagy, inhibit M2 macrophage differentiation, and cause TNF receptor-associated factor 6 (TRAF6) auto-ubiquitination-dependent activation of ASK1, leading to M1 polarization. In M1 macrophages, increased ASK1-TRAF6 interaction induces ASK1 ubiquitination and degradation, switching tumor-associated macrophages (TAMs) from M2 to M1 phenotype and causing tumor regression [45]. Additionally, numerous Chinese medicine monomers including Artemisia leaf extract [56], gypenoside [57], notoginsenoside R1 [58], fisetin [59], and combinations of pseudoephedrine and emodin [60] have been shown in recent studies to significantly improve mitochondrial metabolic function, regulate macrophage polarization states, clear cytotoxic substances, alleviate clinical dysfunction caused by inflammatory reactions or immunosuppression in various organs of sepsis patients, protect nerves, vascular endothelium, and tissues, effectively antagonize sepsis immune imbalance, and inhibit sepsis-induced organ damage.

3.2 Chinese Medicine Compound Formulas

As a traditional and important form of TCM treatment, compound formulas follow the "sovereign, minister, assistant, and courier" compatibility principle, enabling individualized treatment of the same disease with different methods and different diseases with the same method from a holistic perspective [61].

Gegen Qinlian Decoction (Pueraria, Scutellaria, Coptis, Glycyrrhiza) is a classic formula for unresolved exterior syndromes with heat trapped in Yangming,

containing multiple chemical components including flavonoids, saponins, and alkaloids that can resolve the exterior, clear interior, anti-inflammation, inhibit bacteria, reduce glucose and lipids, and provide antioxidant effects [62]. Wang et al. observed that after administering Gegen Qinlian Decoction to non-alcoholic fatty liver mice, expression of various mitophagy proteins both dependent and independent of the Parkin pathway was effectively increased, including Pink, Parkin, LC3B, P62, BNIP3, FUNDC1, autophagy and Beclin-1 regulator 1 (Ambra1), prohibitin 2 (PHB2), and mitochondrial fusion protein 1 (MNF1), while phosphorylated Drp1 expression decreased. Macrophage infiltration markers (F4/80, CD11b) and M1 macrophage polarization markers (CD11c, CCR7) decreased, while M2 macrophage marker (CD163, CD206) protein levels and M2/M1 ratios increased, with significant reductions in pro-inflammatory cytokines and NLRP3 inflammasomes [63].

Daming Capsule (Rheum palmatum, Cassia obtusifolia, Salvia miltiorrhiza, Citrus reticulata, Panax ginseng, Poria cocos) clears heat, reduces turbidity, activates blood, and resolves stasis. Experiments demonstrate this formula can increase expression of the mitophagy receptor nucleotide-binding oligomerization domain-like receptor X1 (NLRX1), reduce mitochondrial and lysosome colocalization and MMP, increase mitochondrial ROS accumulation, activate the SIRT1/AMPK signaling pathway both in vivo and in vitro, inhibit inflammatory responses and oxidative stress in hypoxic stress cardiomyocytes, reduce cardiomyocyte apoptosis, and improve cardiac function in mice [64].

Taohong Siwu Decoction (Persicae semen, Carthami flos, Rehmanniae radix praeparata, Angelicae sinensis radix, Chuanxiong rhizoma, Paeoniae radix) is a traditional formula for activating blood and resolving stasis. Its application significantly increases ATP, MMP, autophagy marker proteins (LC3-II/LC3-I, Beclin1, Atg5), and mitophagy marker proteins (Parkin, PINK1) in oxygen-glucose deprivation/reperfusion (OGD/R)-injured cells, while markedly reducing OGD/R-induced ROS, NLRP3 inflammasomes, and pro-inflammatory cytokines. It protects PC12 cells (a rat pheochromocytoma cell line related to neurons) from OGD/R injury by enhancing mitophagy and inhibiting NLRP3 inflammasome activation, thereby improving cell survival [65].

Liangge San (Rheum palmatum, Forsythia suspensa, Scutellaria baicalensis, Mentha haplocalyx, Gardenia jasminoides, Natrii sulfas, Glycyrrhiza uralensis) excels at purging fire and detoxifying, clearing upper and middle Jiao heat, and purging fire to promote bowel movements. It can attenuate acute inflammation by downregulating glycogen synthase kinase-3β (GSK-3β) mRNA expression in inflammation-related chemotaxis pathways, promoting GSK-3β phosphorylation and inactivation, inducing M1 macrophage polarization to M2, reducing neutrophil infiltration and inflammatory damage, demonstrating anti-inflammatory effects, and representing a promising candidate drug for sepsis treatment [66].

Buyang Huanwu Decoction (Astragalus membranaceus, Angelicae sinensis radix, Paeoniae radix rubra, Chuanxiong rhizoma, Persicae semen, Carthami

flos, Pheretima) is a blood-regulating formula with qi-supplementing, blood-activating, and collateral-dredging effects. High-dose application (20 mg/kg) can significantly reduce cardiomyocyte apoptosis by inhibiting CD45 immune cell infiltration, alleviate the inflammatory microenvironment, and improve survival rates in sepsis mice. Its key molecules paeoniflorin (PF) and calycosin-7-glucoside (CBG) can inhibit NF- B signaling while upregulating TGF-β pathway, alleviating sepsis-induced myocardial injury by inhibiting local macrophage aggregation and immune cell infiltration and promoting M2 macrophage polarization [67].

Yiqi Jianpi Formula (Astragalus membranaceus, Pseudostellaria heterophylla, Angelicae sinensis radix, Ligustrum lucidum, Poria cocos, Atractylodes macrocephala, Citrus reticulata, Scutellaria baicalensis, Glycyrrhiza uralensis) focuses on supplementing spleen qi and nourishing qi-blood. It can improve peripheral blood lymphocyte counts and CD8+ T lymphocyte proportions in acute-on-chronic liver failure (ACLF) rat models, increase pro-inflammatory factors (IL-2, IFN-λ, TNF-α), reduce anti-inflammatory factors (IL-10 and TGF-$ 1), $improveCD8 + Tlymphocytemetabolismandmitochondrialbalance, alleviatelymphocyteimmunedysfunctionbypromotingaut$ 1 $, nuclear respiratory transcription factor 1 (NRF-1), and mitochondrial transcription factor A (TFAM), thereby improving immunosuppression and promoting immune response balance in ACLF rat models [68].

3.3 Acupuncture

Acupuncture, characterized by simplicity, convenience, low cost, and proven efficacy, can improve blood circulation, promote metabolism, regulate immune function, and relieve pain. It has gained worldwide recognition and application in treating various diseases [69-71], with the scientific validity of its meridian theory continuously confirmed [72]. Recent research hotspots include acupoint selectivity, regional specificity, neuroanatomical basis, stimulation intensity, needle depth, and interpretation of measurement results, with increasingly clear neuroanatomical foundations [73]. Numerous studies have found that electroacupuncture stimulation (ES) drives sympathetic pathways in a somatotopic and intensity-dependent manner. Low-intensity ES in hindlimb regions drives the vagal-adrenal axis, producing anti-inflammatory effects dependent on neuropeptide Y (NPY) adrenal chromaffin cells. High-intensity ES in abdominal regions activates NPY splenic noradrenergic neurons through the spinal sympathetic axis. These neurons participate in incoherent feedforward regulatory loops by activating different adrenergic receptors (AR), with ES-induced activation producing anti-inflammatory or pro-inflammatory effects [74].

Regarding sepsis immunomodulation, combined treatment of SP6 (Sanyinjiao) and indomethacin reduces inflammatory cell infiltration, vascular permeability, and myeloperoxidase (MPO) activity in LPS-exposed rats [75]. Our previous research also found that “intestinal three-needle” therapy including Zusanli (ST36), Tianshu (ST25), and Shangjuxu (ST37) can significantly increase in-

testinal flora diversity and beneficial bacterial content, reduce intestinal bacterial translocation, and decrease inflammatory responses by regulating the transient receptor potential vanilloid receptor 1 (TRPV1)/calcitonin gene-related peptide (CGRP) signaling pathway [76]. Zusanli possesses multiple effects including anti-inflammation, immunity enhancement, antioxidant activity, and accelerated gastrointestinal disease recovery. It can significantly reduce TLR4 and NF- B expression, upregulate CD3+, CD4+, and CD8+ lymphocyte expression, restore near-normal CD4+/CD8+ ratios, and control systemic inflammation through vagus nerve activation of dopamine decarboxylase, demonstrating significant efficacy against sepsis-induced heart, lung, kidney, brain, and other organ injuries while substantially improving survival rates in sepsis animals, making it an empirically effective acupoint for enhancing sepsis immunity [77]. Electroacupuncture preconditioning at Hegu (LI4) can significantly attenuate systemic inflammatory responses in lethal sepsis rats by activating muscarinic receptors in the central nervous system, increasing survival rates from 20% to 80%, leading to consideration of this acupoint for preventive treatment of sepsis or perioperative diseases associated with excessive inflammation [78]. Tianshu acupoint shows significant effects in improving gastrointestinal function in sepsis patients [79], while intestinal immune barriers play prominent roles in regulating innate and adaptive immunity [80]. Geshu acupoint has also been proven to alleviate immune inflammation-related cognitive impairment through ES-mediated inhibition of the TLR4/myeloid differentiation primary response protein 88 (MyD88) signaling pathway [81]. Electroacupuncture can improve monocyte (HLA)-DR and T lymphocyte subset (CD3+, CD4+, CD8+, CD4+/CD8+) levels in sepsis patients [82]; mediate analgesic effects through neutrophil recruitment-released β-endorphin [83] or adiponectin (APN)/adiponectin receptor 2 (AdipoR2)-mediated AMPK pathway inhibition of APN short-chain interfering RNA (siRNA) [84]; and effectively target anxiety [85] and depression [86] caused by various diseases. It also reduces recurrence, regulates immune barriers, and improves quality of life in autoimmune diseases such as multiple sclerosis [87] and immune enteritis [88].

Regarding mitophagy, electroacupuncture can significantly increase MMP and ATP in cerebral ischemia-reperfusion (I/R) patients, improve mitochondrial function, reduce neuronal injury, ameliorate autophagy-lysosome pathway (ALP) dysfunction and insufficient mitophagy clearance, and protect cells from neuronal injury in cerebral I/R by clearing nitro/oxidative stress-induced mitochondrial functional damage and reducing accumulation of damaged mitochondria through Pink1/Parkin-mediated mitophagy [89]. It can also promote mitophagy by increasing disrupted-in-schizophrenia 1 (DISC1) expression, enhance amyloid-β clearance, reduce cytotoxicity in hippocampal neurons, and improve learning and memory functions in diabetic rats [90]. Electroacupuncture preconditioning can also protect myocardium from myocardial ischemia-reperfusion injury by inhibiting apoptosis and mitophagy mediated by the mTOR complex 1 (mTORC1)-Unc-51-like autophagy activating kinase 1 (ULK1)-FUNDC1 pathway, reducing ventricular arrhythmia scores and serum

creatine kinase-myocardial band isoenzyme (CK-MB), lactate dehydrogenase (LDH), and cardiac troponin T (cTnT) levels [91].

4. Summary and Prospects

Macrophage polarization represents morphological and functional changes in macrophages under different stimuli, typically classified into M1 and M2 types. Their state transitions play important roles in sepsis autoimmunity. M1 type secretes inflammatory cytokines such as TNF-α and IL-6, enhancing macrophage phagocytosis and antibacterial activity, while M2 type secretes anti-inflammatory factors including IL-10 and TGF-β, mediating cellular repair and tissue remodeling. As an important factor affecting macrophage polarization, dysregulated mitophagy may be a potential cause of sepsis, and interventions targeting mitophagy dysfunction may have therapeutic potential [92]. Both activating and inhibiting mitophagy can positively influence macrophage polarization through bidirectional regulation at different sepsis treatment stages. TCM interventions including herbal monomers, compound formulas, and acupuncture, following treatment principles of supplementing deficiency and purging excess, clearing heat and warming cold, and treating both root and branch, achieve effects of strengthening vital qi, eliminating pathogenic factors, harmonizing yin-yang, dredging meridians, and regulating viscera. By regulating MMP and key mitophagy-related proteins including PINK1, Parkin, LC3, and P62, these therapies modulate macrophage phagocytosis, dynamically balance M1/M2 ratios, affect macrophage cytokine and marker expression, alleviate excessive oxidation, inflammation, and organ dysfunction. They can inhibit cellular inflammatory storms in early sepsis and enhance immunity in late sepsis, providing bidirectional regulation to maintain dynamic physiological balance without excessive hyperactivity or suppression at any disease stage. This achieves prevention and reversal of sepsis progression from toxin-heat blazing syndrome to blood stasis obstruction and acute deficiency syndrome, thereby "intercepting" sepsis progression in advance and offering a novel approach of "preventing disease before onset and preventing progression after onset."

However, current clinical and basic research on TCM prevention and treatment of sepsis immune dysfunction remains limited. Existing limitations include: clinical indicators mostly confined to single time-point changes lacking dynamic monitoring of TCM immunomodulation, and clinical detection methods making it difficult to observe mitochondrial-level indicator fluctuations during disease changes. Therefore, future development should accelerate clinical and basic research progress on TCM regulation of mitophagy affecting macrophage polarization in sepsis immune function, conduct data mining combining network big data with TCM classics to explore effective TCM methods in sepsis immune regulation, and combine large-sample, multi-center clinical dynamic monitoring follow-ups with more extensive and in-depth in vivo and in vitro basic experimental research to discover more diverse and precise pathways and

upstream/downstream molecular mechanisms of TCM regulation of mitophagy affecting macrophage polarization. Furthermore, integration with new technologies such as single-cell sequencing and multi-omics analysis should be pursued to achieve "visualization" of clinical treatment mechanisms of TCM methods, enabling various TCM techniques to achieve truly reliable, convincing clinical applications and providing new perspectives and scientific evidence for TCM in sepsis treatment.

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