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Aberrant parasympathetic responses in acupuncture therapy for restoring immune homeostasis

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Abstract

Acupuncture is an effective therapy used worldwide to treat various diseases, including infections, allergic disorders, autoimmune diseases, and immunodeficiency syndromes. Except for the hypothalamic-pituitary-adrenal axis, acupuncture exerts its regulatory effect mainly by producing autonomic reflexes, including somatic-sympathetic and somatic-parasympathetic reflexes. In this review, we discuss the updated progress of the cholinergic vagal efferent pathway, vagal-adrenal axis, local spinal sacral-parasympathetic pathway, and the somatotopic evocation of parasympathetic responses related to restoring immune homeostasis within acupuncture therapy. Targeting the parasympathetic reflex offers scientific instruction for the design of acupuncture protocols for immunological diseases, providing more specialized comprehensive treatment recommendations.

Key words: Acupuncture, Immunoregulation, Inflammation, Parasympathetic nerve

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Introduction

Acupuncture was invented in China thousands of years ago, and is now a popular alternative therapy in the United States, Europe, and many Asian countries. According to the ancient meridian theory of oriental medicine, acupuncture is the clinical insertion and manipulation of thin needles into specific body sites, also called acupoints. It is thought that the process of acupuncture harmonizes the body's energy and blood flow to induce profound psychophysical responses[1–3]. A series of basic and clinical studies have shown that acupuncture stimulation effectively manages and treats immunological diseases, including allergic disorders[4-5], infections[6-7], autoimmune diseases[8-9], and immunodeficiency syndromes[10-11]. This non-pharmacological and noninvasive approach has attracted the attention of the clinical medicine community and has been advocated by leading researchers[12–16]. Thus, the underlying mechanisms, especially the neuronal networks, are in the process of being explained.

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When assessing the immune-regulatory mechanisms of acupuncture, previous studies have shown that acupuncture deforms connective tissues and directly activates different somatosensory fibers[17-18]; however, acupuncture also induces the secretion of many small molecules in the body's acupoints by activating local cells[19-20], including mast cells, fibroblasts, dendritic Langerhans cells, keratinocytes, and monocytes/macrophages. Moreover, acupuncture activates somatic afferent nerves and transports them to the spinal cord, hypothalamus, and brainstem, including the solitarty tract nucleus (STN), ventral reticular nucleus (VRM), area postrema (AP), and dorsal motor nucleus of the vagus (DMV). When integrating information into the brain, acupuncture evokes multiple neuroimmune reflexes, including vagal-parasympathetic reflexes, sympathetic reflexes, and the hypothalamic-pituitary-adrenal (HPA) axis to release neurotransmitters and hormones that restore immune homeostasis[21]. Peripheral nerve stimulation by acupuncture also induces local reflexes[22–24] such as the somatic-sympathetic-lung reflex and somatic-spinal sacral-parasympathetic-visceral reflex, producing local immunoregulatory effects. Notably, the different somatic reflexes evoked by acupuncture in restoring immune homeostasis are related to stimulation parameters, such as body acupoint selection, stimulation intensity, stimulation depth, and the state of the body.

Several reviews have discussed the role and mechanisms of the sympathetic pathway and HPA axis in acupuncture therapy[25–29], including immunomodulation. In this review, the aberrant parasympathetic responses and the underlying mechanisms of acupuncture therapy for restoring immune homeostasis are discussed in general and based on clinical studies published in the last two decades. In particular, we will focus on (1) the cholinergic vagal efferent pathway, (2) the vagal-adrenal axis, (3) the local spinal sacral-parasympathetic pathway, and (4) somatotopically evoked parasympathetic reflexes for acupuncture treatment of immunological diseases (Figure 1). Finally, we discuss future prospect of this research field.

Cholinergic vagal efferent nerve responses for acupuncture immunomodulation

The cholinergic vagal efferent, which exits from the hindbrain and innervates the thoracic and visceral organs, represents a major branch of the autonomic nervous system for maintaining body homeostasis. Two main cholinergic vagal efferent pathways have been proposed for immunoregulation[30–32]: the cholinergic anti-inflammatory pathway (CAP, the cholinergic vagal-splenic sympathetic pathway) and the cholinergic vagal-myenteric plexus pathway. Both these pathways can be activated by body acupuncture therapy for immunological diseases[33-34].

The cholinergic vagal-splenic sympathetic pathway

The cholinergic vagal-splenic sympathetic pathway, which was first discovered by Borovikova et al. in 2000[35], is a systemic anti-inflammatory pathway mediated by the vagal nerve. In recent years, the understanding of this pathway has gradually improved. For instance, Huston et al. found that after splenectomy, the CAP mediated by the vagal nerve was blocked[36–38], which indicates the important role of the spleen in the CAP. In acupuncture evoked by the cholinergic vagal-splenic pathway, the somatic sensory fiber via the spinal transmits the signal to the NTS and other brain regions and then activates the vagal efferent nerve in the DMV to release acetylcholine (Ach). Acetylcholine acts directly or indirectly via the celiac ganglion on the splenic sympathetic nerve[39], which releases noradrenaline to act on the β2 adrenergic receptors (β2-AR) on choline acetyltransferase (ChAT)$^+$ CD4$^+$T- or B-lymphocytes. ChA T$^+$ CD4$^+$ T- or B-lymphocytes then release acetylcholine to act on the alpha-7 nicotinic receptor (α7nAChR) of splenic macrophages and other immune cells. The final outcome is the prevention of nuclear translocation of the nuclear factor-κB transcription factor (NF-κB), ultimately reducing tumor necrosis factor (TNF)-α, interleukin (IL)-1b, and other pro-inflammatory factors released from macrophages and other immune cells[40-41]. In addition to the anti-inflammatory mechanism of splenic Ach, some studies have shown that noradrenaline released from the splenic sympathetic nerve via its β2-AR induces the release of the anti-inflammatory cytokine IL-10 in T cells, B cells, and macrophages[42–44].

Inspired by the discovery of cholinergic vagal-splenic pathways, several studies have shown that vagus nerve stimulation and limb acupoint stimulation can alleviate immunological diseases through this pathway. For example, Huston et al.[45] found that vagus nerve stimulation can significantly reduce the levels of TNF-α in

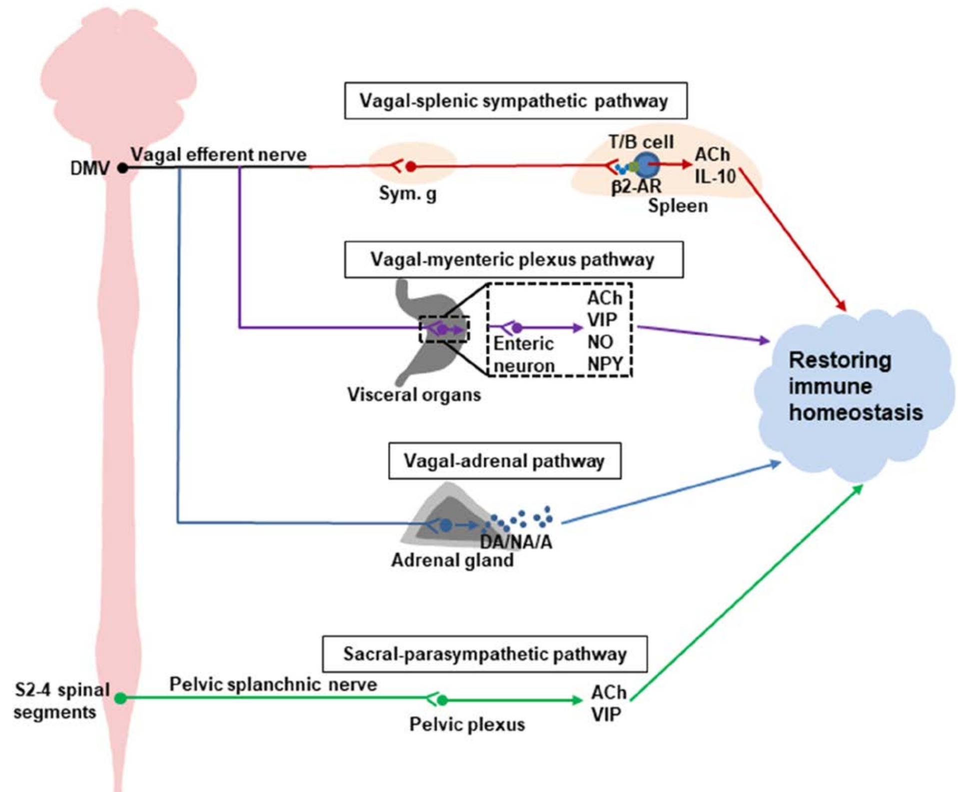

Figure 1. Parasympathetic-associated immunoregulatory pathways in acupuncture therapy. Acupuncture activates the parasympathetic nerve, improves inflammatory response, and restores immune homeostasis through Vagal-splenic sympathetic, Vagal-myenteric plexus, Vagal-adrenal, and Sacral-parasympathetic pathways. β2-AR: β2 adrenergic receptor; A: adrenaline s; ACh: acetylcholine; DA: dopamine; DMV: dorsal motor nucleus of the vagus; IL-10: interleukin-10; NA: noradrenaline; NO: nitric oxide; NPY: neuropeptide Y; Sym. g: sympathetic ganglion; VIP: vasoactive intestinal peptide.

the spleen and liver of endotoxemia and septicemia mice. This anti-inflammatory process depends on the spleen and α7nAChR, vagus nerve stimulation cannot inhibit TNF-α production in splenectomized or α7nAChR-deficient mice. Lim et al.[46] found that acupuncture stimulation of Zusanli (ST36) could reduce TNF-α mRNA and protein levels in the serum and spleen, but splenectomy or vagotomy could reduce this anti-inflammatory effect. Therefore, they believe that acupuncture can ameliorate inflammation through the cholinergic vagal-splenic pathway.

Two decades after the discovery of the cholinergic vagal-splenic immune-regulatory pathway, researchers are optimistic regarding the potential future use of the pathway in helping ease the burden of immunological diseases through the use of acupuncture. With the increasing interest, there is a growing demand to critically evaluate what is known and what is unknown in terms of acupuncture practices related to the pathway in humans. Indeed, the majority of the literature on the cholinergic-splenic immunomodulation pathway evoked by acupuncture in humans involves correlational studies using indirect measures of vagal activity[47]. Although the results of these preliminary studies are inconsistent, they provide guidance and reference for further research. More correlational data will help to clarify the effects of individual differences in vagal activity on inflammation. Clinical trials of acupuncture or vagal nerve stimulation are of great significance for the clinical implementation of acupuncture. With increased correlational research, a clearer understanding of the role of the cholinergic vagal-splenic immunome regulatory pathway in human acupuncture practice can be achieved. This new understanding may contribute to the development of clinical prevention and treatment of immunodeficiency-based diseases.

The cholinergic vagal-myenteric plexus pathway

The cholinergic vagal immunomodulation pathway can act directly through post-parasympathetic neurons (called the myenteric plexus), which are located in the visceral organs, independent of the spleen. Matteoli et al.[48] found that electrical stimulation at the cervical vagus nerve dramatically suppressed the immune responses of the intestinal muscle layer, independent of spleen T cells. The vagal efferent fibers of the DMV activate cholinergic intestinal neurons to release acetylcholine and then activate α7nAChR-expressing intestinal resident macrophages in the intestinal muscle layer to reduce inflammation[48]. Similarly, de Jonge et al. found that vagal nerve stimulation could activate JAK2/STAT3 signals in intestinal macrophages through the cholinergic vagal-myenteric plexus pathway, inhibit the release of TNF-α, IL-6, and other inflammatory factors by macrophages, and improve the inflammatory response caused by postoperative intestinal obstruction[49-50]. In contrast, Simone Langness et al.[51] found that electrical vagal nerve stimulation could activate intestinal glial cells to secrete the trophic factor S-nitrosoglutathione (GSNO), transforming growth factor (TGF), and other substances, reduce the degree of intestinal leukocyte infiltration, improve the pathological changes of the intestinal mucosa in mice injured by ischemia-reperfusion injury, and reduce intestinal permeability.

Electroacupuncture has the same effect as invasive vagus nerve stimulation and can regulate gastrointestinal immune function directly through visceral post-parasympathetic neurons. In one study, Yang et al.[52] found that electroacupuncture stimulation of ST36 could inhibit the expression of the GABAα receptor in DMV cholinergic neurons, thus activating vagal efferent fibers, followed by the activation of α7nAChR-mediated JAK2/STAT3 signaling in macrophages *via* the release of acetylcholine, vasoactive intestinal peptide (VIP), nitric oxide (NO), and neuropeptide Y (NPY), ultimately inhibiting postoperative ileus-induced inflammatory responses. In addition, it has also been reported that electroacupuncture stimulation of ST36 can improve intestinal ischemia-reperfusion injury and pancreatitis through this cholinergic vagal-myenteric plexus pathway[53-54]; thus, it can be speculated that these immune regulatory pathways may be directly mediated by the intestines, independent of the spleen.

Inflammation caused by different diseases can be ameliorated by different mechanisms. It has been reported that in addition to spleen-dependent or intestine-directly mediated cholinergic anti-inflammatory pathways, electroacupuncture can also activate the cholinergic anti-inflammatory axis to act on the pancreas[54], lungs[55], heart[56-57], brain[58], and other organs to ameliorate digestive, respiratory, circulatory, nervous, and other systemic inflammatory diseases. Therefore, the distribution of different cholinergic anti-inflammatory pathways requires further investigation, it is of great significance for the clinical application of electropuncture to reveal the systemic network of the cholinergic anti-inflammatory pathways activated by electropuncture.

The vagal-adrenal anti-inflammatory axis response produced by acupuncture

The vagal-adrenal anti-inflammatory pathway produced by acupuncture was first discovered by Ulloa et al. in 2014[12]. They found that electroacupuncture at ST36 could dramatically increase the serum levels of catecholamines, especially dopamine. In addition, both adrenalectomy and cervical/subdiaphragmatic vagotomy abolished the production of catecholamines and abolished LPS- and cecal ligation and puncture (CLP)-induced systemic septic inflammation. Furthermore, these researchers further demonstrated that D1 receptor agonists suppressed systemic inflammation. Therefore, they believed that electroacupuncture stimulation of ST36 could induce the vagal nerve to activate 3,4-dihydroxyphenylalanine decarboxylase (DOPA decarboxylase) in the adrenal medulla, promote dopamine release, inhibit the production of inflammatory factors, and alleviate peritonitis in mice. Thus, their results revealed a mechanism for regulating inflammation mediated by the vagal nerve and adrenal glands.

In a different study, Liu et al.[59] found that 0.5 mA electroacupuncture stimulation at ST36 could activate a class of PROKR2 neurons with high expression of neurofilament heavy polypeptide (NEFH) in the dorsal root ganglion, which mainly innervates the deep hind-limb fascia. PROKR2 neurons activate the dorsal root neurons of the spinal cord to project upward to the NTS, and then project to the DMV to activate vagal efferent fibers. In addition, vagal efferent fibers may directly project to the adrenal medulla and activate adrenal chromaffin cells to release noradrenaline, adrenaline, and dopamine, thereby producing anti-inflammatory effects[59]. This result elucidates the detailed mechanism of action of the vagal-adrenal axis.

The studies above demonstrated that a vagal-adrenal axis can control systematic inflammation. However, detailed anatomical proof and the role of the DMV in this pathway remains to be described. Tracey et al. previously showed that efferent vagus nerve signals reduced systemic TNF levels through α7nAChR-mediated signaling in the spleen, a mechanism termed "the cholinergic anti-inflammatory" pathway (as described above). However, as shown by Liu et al.,[59] the anti-inflammatory effects of the vagal-adrenal axis activated by electroacupuncture at ST36 do not involve the spleen. It indicates that there may be two parallel pathways that can control systemic inflammation. Furthermore, Tao et al.[60] found that there are various cell subtypes in the DMV, such as those marked by cholecystokinin (Cck), prodynorphin (Pdyn), and other neurotransmitters or neuropeptides. These different subtypes showed a "labeled-line" mechanism for modulating different visceral organs and physiological functions[60]. Therefore, further research is needed to explore which neuronal subtypes in the DMV are responsible for the vagal-splenic sympathetic pathway and vagal-adrenal axis, respectively.

To date, the exact anti-inflammatory role of catecholamines in this pathway has not been elucidated. In one study, Ulloa et al. found that the anti-inflammatory effect of the vagal-adrenal axis involved dopamine released from the adrenal medulla and D1 receptor[12,61–63]. However, the agonist or antagonist of D1 was injected intraperitoneally; therefore, this administration method could not prove that dopamine from the adrenal medulla was responsible for the anti-inflammatory effects. Furthermore, other hormones and molecules can be released from chromaffin cells[64-65]. Therefore, further studies are required to investigate the involvement of chromaffin cells in the vagal-adrenal axis.

In addition to the alleviation of LPS- and CLP-induced systemic inflammation, the vagal-adrenal axis could also attenuate Lyme arthritis[66]. Akoolo et al. determined that the bioluminescent *Borrelia burgdorferi* burden was similar in electroacupuncture- and mock-treated mice. However, they also found a decrease in the number of neutrophils in the joints and in inflammatory cytokine levels throughout the body. These effects demonstrated that the vagal-adrenal axis could attenuate Lyme's arthritis.

The evocation of the local spinal sacral-parasympathetic pathway through acupuncture to modulate pelvic immunological diseases

In addition to the cholinergic vagal-splenic sympathetic pathway and vagal-adrenal axis, several groups have recently discovered a new immune regulation pathway mediated by the spinal sacral-parasympathetic efferent (i.e., pelvic-splanchnic) nerve pathway[67]. Pasricha et al. found that electroacupuncture stimulation of ST36 could improve gastrointestinal function and intestinal mucosal injury in Sprague-Dawley rats (SD rats) with colitis, reduce leukocyte infiltration, and reduce the secretion of TNF-α, IL-6, and other inflammatory factors[68]. Meanwhile, they observed that parasympathetic nerve activity dramatically increased in rats after electrical stimulation of ST36; therefore, they believed that the activation of the vagal efferent nerve released acetylcholine into the colon, thereby mediating this anti-inflammatory process. Their team subsequently found that after electroacupuncture stimulation of the sacral nerve, the clinical manifestations and pathological changes in SD rats with colitis also improved[69]. In their study, the levels of myeloperoxidase (MPO), TNF-α, Substance P, inducible NO synthetase (iNOS), and other inflammatory indicators decreased; in contrast, the M2 macrophage population increased. Meanwhile, sympathetic nerve activity levels decreased, vagal nerve activity levels increased, noradrenaline levels in the plasma decreased, and the levels of acetylcholine in the colon tissue increased[70]. Therefore, we speculate that electrical stimulation of ST36 might activate the sacral nerve or directly activate the vagal nerve to release acetylcholine into the colon, thereby inhibiting the inflammatory response in rats. In their study, Tu et al.[71] obtained the same results of increased vagal activity, decreased sympathetic activity, and reduced inflammation after electrical stimulation of the sacral nerve. They additionally found that these effects were blocked when the proximal sacral or vagal nerve was severed, suggesting that there may be a sacral pathway mediating this process[71]. However, the specific anti-inflammatory pathway following sacral nerve activation remains unclear and requires further research and exploration.

The study of the local effects of local segmental reflexes, such as spinal sacral-parasympathetic nerve reflexes, is a new research direction, which is different from the previous research mainly focused on the systemic effects of acupuncture or other peripheral nerve stimulation on vagal-parasympathetic nerve. Any type of peripheral stimulation might cause both local spinal-sacral-parasympathetic and supra-spinal vagal-parasympathetic reflexes. In addition, local segmental reflexes may act independently or in conjunction with supra-spinal reflexes to ameliorate different immunological diseases. This question is very crucial in the selection of acupoints for clinical therapy. The interactions and mechanisms of local spinal segmental reflexes and supra-spinal reflexes to evoked parasympathetic responses produced by acupuncture will be an important direction of future research.

Somatotopic organization to drive the parasympathetic-associated immunoregulation pathway using acupuncture

Acupuncture stimulation evokes diverse parasympathetic immunomodulation pathways by initially activating somatosensory fibers located around an acupoint.

Somatosensory neurons in the dorsal root ganglia and trigeminal ganglia are crucial for humans and animals in sense touch, temperature, pain, itches, and body positions. Although many advances have been made in understanding how vagal reflexes are triggered by visceral stimuli, very little is known about the organizational rules regarding vagal reflexes evoked by somatosensory stimulation[72-73]. However, a functional connection between the somatosensory and autonomic nervous systems has been recognized for some time. In the 1970s, Sato et al. first discovered body region specificity in driving the gastric vagal reflex in response to painful pinch stimulation, which can be evoked from limb regions such as ST36 but not from abdominal regions such as ST25, which are completely opposite to gastric sympathetic reflexes[74-75]. This somatotopic organization was supported by the presence of acupoint selectivity for electroacupuncture stimulation to drive this gastric vagal reflex, particularly in terms of driving distinct autonomic pathways from different acupoints or body regions that promote or inhibit gastric motility. These findings may help explain how acupuncture works in the treatment of gastric and intestinal diseases.

Apart from gastric motility modulation, a variety of studies found that acupuncture stimulation could restore immune homeostasis by driving a distinct autonomic pathway, such as the parasympathetic pathway described above. Torres-Rosas et al. first reported that electroacupuncture stimulation (4V, 10 Hz) at ST36 produced an anti-inflammatory effect that was dependent on vagal reflexes and the release of catecholamines, especially dopamine from the adrenal gland. These electroacupuncture stimulation parameters are dependent on local transient receptor potential vanilloid 1 $(TRPV1)^{+}$ sensory fibers to evoke the vagal-adrenal anti-inflammatory axis[12]. Recent studies using genetic manipulation strategies have demonstrated that NPY^{DBH+} chromaffin cells are involved in this anti-inflammatory axis[76]. The results found that low-intensity electroacupuncture stimulation (0.5 mA) with $PROKR2\text{-}Cre^{+}$ sensory neurons could evoke this vagal-adrenal axis from the hindlimb ST36 acupoint. However, either low-intensity (0.5 mA) or high-intensity electroacupuncture stimulation (3 mA) of ST25 activated vagal-parasympathetic efferent neurons located in the DMV, demonstrating acupoint selectivity in driving the vagal reflexes[59]. Activation of this vagal-adrenal axis sufficiently attenuates LPS- and CLP-induced systemic inflammation and this reflex is independent of the disease state and exerts anti-inflammatory effects both before and after cytokine storm peaks. Thus, electroacupuncture stimulation can activate different parasympathetic pathways and ameliorate systemic inflammation in ways dependent on acupoint selection, stimulation intensity, and disease state.

Perspectives and conclusions

As discussed above, the role of acupuncture in resolving immune homeostasis through aberrant parasympathetic responses is supported by numerous clinical trials and animal studies. However, many unsolved gaps remain to be identified. For example, more detailed research is needed on acupoint selection and other stimulation parameters for somatotopically driving different parasympathetic responses to restore immune homeostasis. Additionally, the diverse parasympathetic response time window of acupuncture effect merits further systematic research, including identifying acupuncture effects during different developmental stages of immunological diseases. This should additionally be combined with acupoint selection and stimulation parameters. In addition, further refining and deepening of our understanding regarding the bidirectional regulatory effect and mechanism of acupuncture in immune regulation are required. Acupuncture can suppress immune response in inflammatory diseases and also relieve immune suppression in immune-paralysis diseases such as malignant cancer[77] and HIV. It has been reported that acupuncture can activate natural killer (NK) and $CD8^{+}$ T cells[77-78], regulate the balance of TH1/TH2[79] and regulatory T cell (Treg)/TH17 cell, and promote mast cell degranulation[80] to activate the body's immune response. Based on the above immune regulatory mechanisms, acupuncture can be used to ameliorate tumor immune microenvironment and improve the immunosuppressive state of malignant tumor patients, which is an ideal and promising treatment program. In the future, we need to further investigate the roles and mechanisms of parasympathetic nerve in immune activation and its specific impact on immune-paralysis diseases. Due to our limited understanding of the mechanisms of how acupuncture drives the parasympathetic responses and the feasibility of acupuncture modulating immune homeostasis in clinical application, further researches and clinical trials of acupuncture mechanisms are needed.

Modern neuroanatomical studies have revealed that acupuncture stimulation can drive various somatosensory-parasympathetic pathways in an acupoint- and intensity-dependent manner. Based on LPS-induced systemic inflammation in mice, aberrant parasympathetic responses evoked by acupuncture could be a disease-state-independent mechanism that modulates immunological disease progression. Therefore, somatotopically driving this pathway will ultimately help to improve the efficacy and safety of acupuncture practice and its clinical promotion.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

Jing Liu drafted the original manuscript, and Shun Dong and Shenbin Liu edited the manuscript. All authors have read and approved the final manuscript.

Ethical approval of studies and informed consent

Not applicable.

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Data Availability

All data generated or analyzed during this study are included in this published article.

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