Proceedings of ICBioMed 2026 Symposium: Biomedical Engineering and Smart Medicine
DOI: 10.54254/2753-8818/2026.HZ38239

Mechanism Research Progress of Acupuncture Regulating Vagus Nerve-Cholinergic Anti-inflammatory Pathway in the Prevention and Treatment of Endometriosis-Related Pain

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Abstract. Endometriosis (EM)-related pain involves multiple links including local inflammatory microenvironment, neurogenic inflammation, peripheral and central sensitization, and autonomic nervous imbalance. Current hormone therapy and surgical treatment cannot achieve sufficient pain relief and are prone to recurrence. This paper reviews the role of the vagus nerve-mediated cholinergic anti-inflammatory pathway (CAIP) in EM pain and the mechanistic evidence that acupuncture regulates this pathway. It proposes that CAIP impairment in EM may exist at two levels simultaneously: reduced central vagal efferent tone and downregulated expression of local α7 nicotinic acetylcholine receptor (α7nAChR) in peripheral lesions. Patients with EM have decreased vagal tone which correlates with pain severity. Vagus nerve stimulation can slow lesion progression and improve hyperalgesia in animal models, and α7nAChR agonists can inhibit lesion formation and fibrosis. Electroacupuncture activates the vagus-adrenal axis or spleen-dependent CAIP via acupoints such as Zusanli to exert anti-inflammatory effects, with selectivity for acupoints and stimulation parameters. It is thus inferred that simply enhancing upstream vagal input may be inadequate. Combined strategies that raise vagal efferent tone while improving local receptor reactivity in lesions deserve exploration. Future work shall optimize acupuncture parameters using dedicated EM models and design rigorous clinical trials for mechanistic verification.

Keywords: endometriosis, acupuncture, vagus nerve, cholinergic anti-inflammatory pathway, pain mechanism

1. Introduction

1.1. Disease burden and treatment demand of EM-related pain

EM is a common chronic inflammatory disease among women of reproductive age, pathologically characterized by viable endometrial tissue appearing outside the uterine cavity and myometrium [1]. Its prevalence among reproductive-age women is approximately 6%–10%, and can reach 30%–50% in infertile populations [1]. Pain is one of the most prominent clinical symptoms of EM, manifesting as dysmenorrhea, chronic pelvic pain, deep dyspareunia, defecation pain and other forms [2]. Such

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DOI: 10.54254/2753-8818/2026.HZ38239

pain often progresses gradually, and its severity is not fully parallel to lesion size and r-AFS stage. Pain persists or recurs repeatedly in some patients after combined surgical and pharmacological treatment, seriously impairing work capacity, social function and mental health, and creating substantial disease burden and socioeconomic costs [3]. Effective pain control serves as one core clinical goal to improve the quality of life for EM patients.

1.2. Pathogenesis of em-related pain: from peripheral inflammation to central sensitization

The onset of EM-related pain involves a multi-stage process of peripheral inflammation initiation, neurogenic amplification and consolidated central sensitization: the persistent inflammatory microenvironment and active nerve fiber neoformation within lesions form a positive feedback loop of neurogenic inflammation. Sustained nociceptive afference further induces peripheral sensitization as well as central sensitization in the spinal cord and higher brain regions; detailed mechanisms are presented in Chapter 2. This multi-level, dynamically evolving pathological picture suggests that the maintenance and chronification of EM pain may involve complex interactions between inflammation and neural plasticity. Therapeutic strategies that merely block a single local link often fail to achieve long-lasting efficacy [4].

1.3. Limitations of current treatments and proposal of new directions

Current pharmacological treatments for EM-related pain mainly rely on hormonal preparations including combined oral contraceptives, progestogens and gonadotropin-releasing hormone agonists/antagonists [5]. Although these drugs can relieve pain to a certain extent, their targets focus on hormones or terminal inflammatory mediators. They cannot cover the complete pathological cascade of EM pain from peripheral inflammation initiation, neurogenic amplification to consolidated central sensitization. Relapse occurs easily after drug withdrawal, and long-term use brings adverse reactions associated with hypoestrogenism, such as reduced bone mineral density and vasomotor symptoms. The above limitations of these drugs prevent full coverage of the complete pathological cascade of EM pain [3]. Surgical treatment can resect lesions and release adhesions, yet postoperative recurrence rates remain high, and repeated surgeries carry risks of impaired ovarian reserve function [6]. These clinical dilemmas indicate that effective intervention for EM-related pain may need to go beyond simple hormonal suppression or local lesion resection, and turn to interventions targeting more upstream or integrated links such as neuro-immune interaction networks and autonomic nervous regulation.

Against this background, the role of the autonomic nervous system in EM pain has attracted growing attention. Heart rate variability (HRV) studies indicate that EM patients have reduced vagal tone, and vagal activity is negatively correlated with pain severity [7, 8]. Animal experiments further demonstrate that intact vagus nerve exerts protective effects in limiting lesion growth and pain sensitization [7]. As an important pathway for the nervous system to regulate peripheral immune responses, CAIP has been proven to perform endogenous inflammatory regulation in multiple inflammatory diseases [9, 10]. These findings raise a promising possibility: restoring impaired CAIP function in EM patients by enhancing vagal activity may constitute a new therapeutic approach.

1.4. Entry point of acupuncture and review objectives of this paper

Acupuncture, a long-standing pain intervention modality, has gained relatively clear advances in its anti-inflammatory and analgesic mechanisms at neuroanatomical and neuroimmunological levels in

DOI: 10.54254/2753-8818/2026.HZ38239

recent years [11]. Studies represented by electroacupuncture show that stimulation of specific acupoints can exert systemic anti-inflammatory effects by activating the PROKR2 sensory neuron-mediated vagus-adrenal axis or spleen-dependent CAIP. Among these, research on Zusanli ST36 in the hind limb is the most comprehensive [12, 13]. Such effects are closely associated with stimulation parameters including acupoint selection, stimulation intensity and frequency, and their neuroanatomical basis is reproducible [14, 15]. These findings provide mechanistic plausibility for acupuncture to intervene in EM-related pain via CAIP. Nevertheless, research in this field remains in its initial stage, direct evidence from EM models is limited, and clinical translation still faces considerable gaps.

This paper aims to systematically sort out the pathological mechanisms of EM-related pain, correlative evidence of CAIP in EM, and progress in experimental studies on the anti-inflammatory and analgesic effects of acupuncture through this pathway. On this basis, it analyzes the strength and deficiencies of existing evidence, and puts forward preliminary prospects for future research directions.

2. Pathological mechanism basis of EM-related pain

2.1. Local inflammatory microenvironment and neurogenic inflammation

EM lesions are essentially chronic inflammatory lesions formed within the abdominal cavity microenvironment [3]. Cyclic bleeding, shedding of ectopic endometrium and impaired clearance of tissue debris continuously activate local innate and adaptive immune responses [16, 2]. Concentrations of pro-inflammatory factors including TNF-α, IL-1β, IL-6 and PGE_2 in peritoneal fluid and lesion sites of EM patients are higher than those in control groups [16, 17]. On one hand, these factors directly stimulate sensory nerve endings around lesions to generate pain signals; on the other hand, they raise cyclooxygenase-2 expression and prostaglandin synthesis, lowering local pain threshold [18, 19].

EM lesions also exhibit active nerve fiber neoformation [20]. In the basal part of lesions and surrounding connective tissues, a large number of sensory nerve fibers expressing SP and CGRP as well as sympathetic nerve fibers expressing tyrosine hydroxylase proliferate abnormally, forming a dense neural network [21, 16]. These newly formed nerve fibers not only transmit pain signals, and the neuropeptides they release can conversely act on the local immune microenvironment: SP promotes mast cell degranulation and macrophage activation [16], CGRP modulates the function of antigen-presenting cells, and NGF further facilitates nerve fiber growth and sensitizes nociceptors [22]. This positive feedback loop — immune cells release inflammatory factors → stimulate nerve endings to secrete neuropeptides → neuropeptides further activate immune cells — namely neurogenic inflammation, serves as a critical mechanism for self-sustaining and amplifying EM pain [23]. Macrophages occupy a core position in this loop [16]. Their M1/M2 polarization imbalance can impair inflammation resolution [16], and directly drive nerve fiber hyperplasia by secreting neurotrophic factors such as NGF [22].

2.2. Peripheral sensitization and central sensitization

Persistent pain originates not merely from local noxious stimuli but also from plastic changes within the sensory conduction pathway itself [24]. At the peripheral level, inflammatory mediators such as PGE_2, NGF and bradykinin in EM lesions and adjacent tissues [17, 22] can reduce the activation threshold of nociceptors on primary sensory neurons in the dorsal root ganglion (DRG) [25]. The

DOI: 10.54254/2753-8818/2026.HZ38239

specific mechanism involves the binding of NGF to its receptor TrkA, which upregulates the expression and functional activity of transient receptor potential vanilloid subtype 1 (TRPV1) and acid-sensing ion channels, increasing the sensitivity of sensory neurons to mechanical and thermal stimuli. Elevated expression of SP and CGRP in DRG is also observed in EM models, indicating their potential participation in the amplification of peripheral afferent signals. Such peripheral sensitization renders originally non-noxious stimuli perceived as pain by the central nervous system, including mild traction and normal peristalsis of pelvic viscera. Peripheral sensitization is an important mechanism underlying chronic pelvic pain and deep dyspareunia in EM patients [2].

At the central level, sustained nociceptive afferent input from pelvic viscera can induce central sensitization of spinal dorsal horn neurons [24]. Inflammatory mediators and neuropeptides activate spinal glial cells, including microglia and astrocytes, to promote the release of IL-1β, TNF-α and brain-derived neurotrophic factor, altering synaptic transmission efficiency of spinal dorsal horn neurons. Its manifestations include enhanced excitatory transmission, attenuated inhibitory transmission, expanded receptive fields and elevated responsiveness to non-noxious stimuli [26, 27]. Spinal central sensitization abnormally amplifies the ascending transmission of pain signals [28]. Long-term central sensitization can trigger functional remodeling of higher brain regions such as the thalamus, anterior cingulate cortex and insula, transforming pain from a pure sensory experience into a comprehensive state involving emotional, cognitive and autonomic responses [6]. This is recognized as the neural basis for the chronification and incomplete reversibility of EM-related pain [4].

2.3. Autonomic nervous imbalance: sympathetic overactivity and impaired vagal tone

The autonomic nervous system plays a vital role in regulating visceral sensation and local immune status, and EM patients present marked autonomic dysfunction [29]. Previous studies have focused more on sympathetic nervous system activation. Increased norepinephrine levels in plasma and peritoneal fluid and higher density of sympathetic nerve fibers around lesions have been detected in EM patients [29], suggesting that excessive sympathetic activation may participate in lesion progression by boosting inflammatory responses and angiogenesis [30]. The other branch of the autonomic nervous system is the parasympathetic nervous system, whose principal component is the vagus nerve. Nevertheless, the role of the vagus nerve in EM pathological processes has long been underappreciated.

HRV is a commonly used non-invasive indicator to quantify autonomic function, and systematic reviews have supported its value in assessing chronic pain and fatigue-related symptoms [31]. High-frequency HRV is a classic marker reflecting vagus-mediated respiratory sinus arrhythmia. Multiple studies report that HF-HRV of EM patients is lower than that of healthy controls, indicating generally reduced vagal tone [7, 8, 29]. The study by Moreira et al. [8] shows that lower resting vagally mediated HRV parameters correlate with higher chronic pelvic pain scores in patients, demonstrating a quantitative association between impaired vagal function and pain severity. Hao et al. [7] validated these findings in human subjects and further proved in animal experiments that vagotomy aggravates lesion growth and hyperalgesia in EM model mice, while VNS can retard lesion progression and improve pain behaviors. This provides experimental evidence supporting the causal role of low vagal function in EM pain. These findings upgrade autonomic imbalance from a mere accompanying phenomenon to a pathological mechanism, and also lay a theoretical foundation for acupuncture to exert therapeutic effects by enhancing vagal tone.

DOI: 10.54254/2753-8818/2026.HZ38239

3. Association between CAIP and EM

3.1. Basic mechanism of CAIP

CAIP represents one of the important discoveries in neuroimmunology in recent years, revealing an anatomical pathway by which the nervous system modulates peripheral immune responses through vagal efferent signals [9]. This pathway starts when peripheral inflammatory signals are transmitted via vagal afferent fibers to the nucleus tractus solitarius (NTS). After integration in brainstem nuclei, efferent commands are then dispatched from the dorsal motor nucleus of the vagus and nucleus ambiguus. This "inflammatory reflex" framework constitutes the central foundation of CAIP [9, 32, 33].

At the efferent segment, the vagus nerve does not directly reach all peripheral immune organs, but mediates immune regulation through the "vagus-spleen" pathway [34]. Acetylcholine released from the terminals of vagal efferent fibers activates α7nAChR on the surface of macrophages in the spleen [35], and this receptor is also expressed on immune cells such as T cells [36]. Activation of α7nAChR inhibits nuclear translocation of nuclear factor κB through intracellular signaling cascades including JAK2 and STAT3, thereby reducing the capacity of macrophages to produce pro-inflammatory factors such as TNF-α, IL-1β, IL-6 and IL-18 under Toll-like receptor stimulation [37]. In addition, acetylcholine-expressing T cells in the spleen serve to amplify and transmit vagal signals within this pathway [36]. Characterized by its modulatory function, this pathway keeps inflammatory response intensity below the threshold of tissue damage without completely eliminating immune responses [10, 38]. Studies by Pavlov et al. have confirmed that brain acetylcholinesterase activity can suppress peripheral inflammation via CAIP [39]. Nevertheless, it remains unclear whether the effector organs of this pathway involve the local abdominal immune microenvironment, and its potential significance in EM, a focal inflammatory disease of the abdominal cavity, awaits further exploration.

3.2. Evidence of impaired vagal tone in EM patients

Based on the theoretical framework of CAIP, reduced vagal tone in EM patients may signify more than an isolated change in autonomic function; it may indicate impaired CAIP-mediated inflammatory regulation [29]. Hao et al. [7] compared laparoscopically confirmed ovarian EM patients with healthy controls using time-domain and frequency-domain HRV analyses. The EM group exhibited lower root mean square of successive RR interval differences (RMSSD), pNN50 and normalized high-frequency power, alongside an elevated LF/HF ratio, which suggested a shift of the sympathetic-vagal balance toward sympathetic dominance. However, no significant correlations were found between these HRV indices and rASRM scores, menstrual phase or dysmenorrhea severity in this study. Therefore, a dose-effect relationship between vagal tone and disease activity cannot be determined solely from these results. Moreira et al. [8] found that vagally mediated HRV parameters were negatively correlated with pain severity, implying that impaired vagal function may act as an independent influencing factor for EM pain severity. This inference still requires verification through large-sample regression analyses. A mindfulness intervention study from the same research group [40] further demonstrated that vagally mediated HRV could change following intervention and was associated with self-regulatory capacity in patients with EM-related chronic pain. Still, the interventional design of this study cannot directly establish a causal link between HRV and pain perception.

DOI: 10.54254/2753-8818/2026.HZ38239

Such correlational studies indicate that low vagal tone coexists with EM pain, yet causality cannot be confirmed. Hao et al. [7] performed causal validation within the same study using a mouse EM model. Surgical cervical vagotomy markedly increased the weight of ectopic lesions, lowered E-cadherin expression while raising vimentin and α-smooth muscle actin expression inside lesions, aggravated fibrosis, and shortened paw withdrawal latency in the hot-plate test. These findings show that intact vagus nerve exerts inhibitory effects on EM lesion progression and pain sensitization. By contrast, auricular vagus nerve stimulation (auricular VNS) significantly reduced lesion weight, retarded lesion progression and fibrosis, and ameliorated hyperalgesic behaviors. These bidirectional manipulation experiments provide evidence for the active involvement of the vagus nerve in the regulatory network of inflammation and pain in EM [7].

3.3. Roles of local α7nachr in lesions

The final effector step of CAIP is the binding of acetylcholine to α7nAChR. The expression status and function of this receptor within EM lesions directly determine the local efficacy of CAIP. Hao et al. [41] used immunohistochemistry to detect α7nAChR expression in ovarian and deep infiltrating EM lesions. Immunostaining intensity was significantly weaker than that in normal endometrium, and lesion α7nAChR staining levels were negatively correlated with both lesion fibrosis and dysmenorrhea severity, indicating local receptor downregulation within lesions. Even if systemic vagal efferent signals remain normal, suppressed local receptor expression in lesions may weaken the anti-inflammatory input. In functional experiments, administration of the selective α7nAChR agonist PNU-282987 to EM mice reduced lesion weight and fibrosis, and prolonged hot-plate withdrawal latency [41]. This study further revealed that the α7nAChR agonist inhibited activated platelet-induced epithelial-mesenchymal transition, fibroblast-myofibroblast transition and smooth muscle metaplasia, and decreased contractility and collagen production of ectopic endometrial stromal cells [41]. These results suggest that α7nAChR may participate in the chronic fibrotic progression of lesions. Research by Yamada-Nomoto et al. [42] confirmed that α7nAChR agonists suppressed LPS-induced IL-1β expression in human peritoneal macrophages and markedly inhibited lesion formation in mouse EM models. Keever et al. [30] reviewed neuroimmune modulation by α7nAChR in inflammatory diseases. Although this review is not dedicated to EM, it offers references for understanding the implications of local receptor downregulation in lesions. From the perspective of the complete CAIP cascade, pathway impairment in EM may occur simultaneously at two levels: attenuated central vagal efferent signals and downregulated α7nAChR expression in peripheral lesions. This conclusion carries direct implications for intervention strategies. Simply enhancing upstream vagal input (such as VNS or taVNS) may not suffice to restore pathway efficacy. Combined strategies that raise vagal efferent tone while improving local receptor responsiveness in lesions may be more reasonable, and also provide two separately testable regulatory nodes for acupuncture research.

4. Mechanistic evidence for acupuncture activating CAIP

4.1. Experimental evidence that acupuncture or electroacupuncture drives the vagus-adrenal axis

The anti-CAIP activation effect of acupuncture was first identified in experiments using sepsis models. Torres-Rosas et al. [13] observed in mouse models of polymicrobial peritonitis and endotoxemia induced by cecal ligation and puncture that electroacupuncture stimulation at hindlimb

DOI: 10.54254/2753-8818/2026.HZ38239

ST36 reduced serum levels of TNF-α, IL-1β and IL-6 and improved animal survival rate. This anti-inflammatory effect did not rely on the classic spleen and α7nAChR cascade, but depended on the adrenal gland; adrenalectomy abolished this effect. Its mechanism lies in vagal efferent signals driving the adrenal medulla to release dopamine, which acts on D1 receptors to inhibit macrophage inflammatory responses. This pathway is termed the vagus-adrenal axis. Trevizan-Baú and McAllen [43] questioned the anatomical premise of this pathway, arguing that evidence supporting direct vagal parasympathetic efferent innervation of the adrenal gland is weak and likely arises from technical artifacts, while evidence for direct vagal afferent innervation of the adrenal gland is more robust. Accordingly, the anatomical basis for the efferent segment within the vagus-adrenal axis remains controversial. This controversy suggests that when extrapolating acupuncture mechanisms for EM intervention, an open stance should be maintained regarding whether effects arise from efferent cholinergic innervation or afferent signals mediated via central reflexes. These findings localize the anti-inflammatory mechanism of electroacupuncture to a specific neuroanatomical pathway, indicating that acupuncture can achieve immune regulation via multiple vagus-dependent downstream effectors.

In 2021, Liu et al. [12] used neural tracing and optogenetic manipulation to systematically dissect the neuroanatomical basis for low-intensity electroacupuncture at ST36 to activate the vagus-adrenal axis. The study found that PROKR2-positive sensory neurons within the ST36 acupoint region are activated upon electroacupuncture stimulation, and their afferent signals drive catecholamine release from the adrenal medulla through a spinal cord-brainstem-vagal efferent circuit [12]. This work further revealed the relationship between acupoint specificity and stimulation intensity: effects of electroacupuncture at ST36 are tightly linked to stimulation intensity. Low-intensity stimulation, such as 0.5 mA, selectively activates PROKR2 neurons and triggers the vagus-adrenal axis. High-intensity stimulation, for instance 3.0 mA, can elicit spinal sympathetic reflexes at both hindlimb ST36 and abdominal Tianshu (ST25), with NPY-positive sensory neurons forming the afferent arm; this pathway differs from the vagus-adrenal axis activated by low-intensity stimulation. This discovery provides a neuroscientific explanation for acupoint selection and stimulation parameters in acupuncture [15], and also supplies experimental evidence for parameter selection in acupuncture for chronic inflammatory disorders such as EM [12]. Other reviews have outlined the overall framework of acupuncture effects from a neuroimmunomodulatory perspective [11].

4.2. Acupoint selection and stimulation parameters

Acupoint selection, stimulation intensity and depth constitute core variables in clinical acupuncture practice, and experimental studies have examined how these factors influence CAIP activation [14]. As the He-sea point of the Stomach Meridian of Foot-Yangming, ST36 is widely used in acupuncture analgesia and immune modulation. Its deep anatomical location corresponds to the tibialis anterior muscle and branches of the deep peroneal nerve, forming one region enriched with PROKR2 sensory neurons [12]. The study by Liu et al. [12] demonstrated that low-intensity electroacupuncture at ST36 activates the vagus-adrenal axis, whereas abdominal Tianshu (ST25) and other sites with sparse PROKR2 neuron distribution fail to produce this effect. Following the same distribution pattern, Shousanli (LI10) on the upper limb was predicted and experimentally validated to yield comparable effects, showing that the functional selectivity of acupoints has a neuroanatomical foundation [15]. Stimulation depth also affects outcomes: superficial insertion limited to subcutaneous tissue cannot activate deep PROKR2 neurons, while deep penetration reaching the muscular layer generates effective afferent signals [12]. Yang et al. [44] systematically

DOI: 10.54254/2753-8818/2026.HZ38239

reviewed the role of acupuncture in modulating the autonomic nervous system in chronic inflammatory diseases.

Within the specific context of EM research, studies on acupuncture parameters using EM models remain limited, yet research on transcutaneous auricular vagus nerve stimulation (taVNS) offers references [45]. taVNS stimulates terminal branches of the auricular vagus nerve in the outer ear skin to directly trigger vagal afferent signals, which produce efferent effects after integration within the nucleus tractus solitarius [45]. Although taVNS initiates afferent input at a different site from body acupuncture at ST36, both recruit the nucleus tractus solitarius and brainstem autonomic neural networks at the central integration level. The CAIP-activating effects of taVNS can partly provide proof-of-concept for body acupuncture targeting EM via vagal pathways [45]. Hao et al. [7] observed reduced vagal tone among EM patients and accordingly proposed taVNS as a potential intervention. A subsequent pilot trial conducted by Nie et al. [46] preliminarily showed that taVNS relieved dysmenorrhea in patients with adenomyosis and EM, indicating the therapeutic potential of non-invasive vagal activation for this disease. Nevertheless, this trial had a small sample size and lacked rigorous blinded controls, so conclusions await further validation. Body acupuncture at ST36 and taVNS may differ in pathway emphasis: the former engages a more complex spinal-brainstem circuit, whereas the latter acts more directly on vagal afferents [47]. The relative merits and complementary relationship between these two approaches in EM require further investigation.

4.3. Cross-disease indirect evidence for acupuncture-mediated CAIP activation

As a conserved neuroimmune pathway, CAIP's role in acupuncture-induced anti-inflammatory responses has been validated in multiple disease models. Such cross-disease indirect evidence provides references for translation to EM. In sepsis models, beyond the studies by Torres-Rosas et al. [13] and Liu et al. [12], Zhang et al. [48] found that the anti-inflammatory effect of electroacupuncture at ST25 is mediated by adrenal sympathetic nerves. This suggests that besides CAIP and the vagus-adrenal axis, sympathetic pathways can also participate in acupuncture anti-inflammation; different acupoints and stimulation parameters may mobilize distinct neuroendocrine pathways. In an acute pancreatitis model, Zhang et al. [49] reported that electroacupuncture intervention lowered serum amylase and lipase activity, alleviated pancreatic histological injury, and reduced serum TNF-α and IL-6 concentrations. This effect similarly depended on intact vagus nerve function. Furthermore, existing reviews have summarized evidence for acupuncture exerting anti-inflammatory effects by regulating the autonomic nervous system across various chronic inflammatory disorders [44].

Several considerations should be taken into account when translating this indirect evidence to EM [50]. First, EM pain involves complex neuroplastic alterations of peripheral and central sensitization [24, 27], yet most anti-inflammatory studies use histopathology and serum inflammatory cytokines as endpoints, lacking systematic assessment of pain behaviors [47]. Second, available supporting evidence mainly originates from electroacupuncture experiments; manual acupuncture studies are relatively scarce. Clinically, EM patients mostly receive manual acupuncture or combined manual-electroacupuncture therapy [51], and uncertainties remain regarding parameter translation between these modalities [11]. Therefore, while indirect evidence supports the mechanistic plausibility of acupuncture targeting EM through CAIP, direct and systematic validation using EM models is still required.

DOI: 10.54254/2753-8818/2026.HZ38239

5. Conclusion and outlook

This paper systematically reviews the pathological mechanisms of EM-related pain, correlative evidence of CAIP in EM, and research progress of experimental studies on acupuncture activating this pathway. Existing evidence demonstrates that: (1) EM-related pain involves multi-level pathological alterations including local inflammatory microenvironment, positive feedback of neurogenic inflammation, and peripheral and central sensitization [16, 17, 24, 26]. Autonomic imbalance, especially impaired vagal tone, is regarded as one upstream regulatory factor of the above pathological network [7, 29]; (2) EM patients exhibit reduced vagal nerve activity, and low vagal function correlates with aggravated pain [8, 40]. Animal experiments confirm that vagotomy exacerbates lesions whereas VNS can retard disease progression [7], and suppressed α7nAChR expression at lesion sites may further weaken the terminal efficacy of CAIP [41, 42]; (3) Acupuncture exerts anti-inflammatory effects by activating the PROKR2 sensory neuron-vagus-adrenal axis or spleen-dependent CAIP [12, 13]. Acupoint selection and stimulation intensity confer selectivity on pathway activation [14, 15]. taVNS and cross-disease indirect evidence provide references for acupuncture intervention of EM via CAIP [7, 45, 47].

Several unresolved challenges remain in this research field. First, direct evidence linking CAIP to EM mainly comes from studies by Hao et al. [7, 41]. Replication and verification in EM models with diverse genetic backgrounds are still required [1]. Second, the effects of acupuncture-mediated CAIP activation are tightly associated with stimulation parameters, yet systematic screening of optimal stimulation protocols for EM remains inadequate. Parameter optimization studies focusing on primary endpoints including pain behavior, lesion volume and local inflammatory factors, combined with autonomic function indicators such as HRV [31], can lay foundations for subsequent clinical trials [51]. Third, it remains unclear whether downstream effects of CAIP solely rely on α7nAChR or involve synergism between α7nAChR and the vagus-adrenal axis, and whether pathway switching occurs across distinct EM stages [52]. Combining conditional knockout mice and chemogenetic manipulation [35, 37] to dissect contributions of different CAIP branches at various pathological stages of EM will facilitate understanding of the dynamic regulatory characteristics of this pathway [10]. Fourth, current studies on acupuncture regulating CAIP for EM treatment are predominantly based on animal models, with insufficient evidence for clinical translation [11]. Given that non-invasive stimulation of vagal afferents has undergone preliminary clinical exploration in populations with chronic pelvic pain [45], designing randomized controlled trials to collect serum inflammatory factors, HRV indices, pain scores and quality-of-life data synchronously before and after acupuncture treatment [7, 8], and applying mediation analysis to test the existence of the causal chain "elevated vagal activity → decreased inflammatory factors → pain relief" in human subjects [30], will help promote the translation of this field from mechanistic research toward clinical application.

In summary, acupuncture-mediated CAIP regulation offers a neuroimmunologically grounded intervention strategy for the treatment of EM-related pain. A gap still exists from mechanistic validation to clinical application in this field. Nevertheless, the above research directions hold promise to advance acupuncture from empirical therapy toward mechanism-driven precise strategies [50].

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