Acupuncture and Herbal Medicine

Acupoints as state-dependent neuroimmune gateways: insights from stress-responsive neuroimmune circuits

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A specialized sympathetic-eosinophil circuit in stress-induced inflammation

Psychological stress is widely recognized as an important aggravating factor in atopic dermatitis (AD)[1], yet the biological pathways that translate central stress perception into peripheral inflammation remain unclear. Tian et al.[2] identified a specialized neuroimmune circuit in which prodynorphin-expressing (Pdyn$^+$) sympathetic neurons regulated eosinophil-mediated skin inflammation under stressful conditions. The authors further supported this mechanism with clinical observations showing that perceived stress levels correlated with disease severity indices (including SCORing Atopic Dermatitis [SCORAD] and numeric rating scale [NRS]) and eosinophil abundance in both blood and lesional skin, whereas other immune populations remained largely unchanged. This selective association provides clinically relevant support for the pathways identified in murine models.

The study also showed that peripheral sympathetic activity, rather than hypothalamic–pituitary–adrenal (HPA) axis signaling, exacerbated stress-induced inflammation. Adrenalectomy worsened the dermatitis, suggesting that glucocorticoids counterbalanced the anti-inflammatory effect. At the mechanistic level, Pdyn$^+$ noradrenergic sympathetic neurons recruited eosinophils *via* the CCL11–CCR3 axis and activated them through β2-adrenergic receptor (Adrb2) signaling. In contrast, Npy$^+$ sympathetic neurons regulated the vascular tone without contributing to eosinophilic inflammation. This cell type–specific organization offers a plausible explanation for how psychological stress can produce spatially restricted and immunologically selective inflammatory responses[2].

Redefining acupoints as state-dependent neuroimmune gateways

Although acupuncture has not been directly examined, our findings provide a biological context for emerging concepts in acupuncture research and traditional East Asian medicine. Acupoints have long been used as therapeutic targets and diagnostically reactive sites that reflect the internal pathological states[3–4]. To date, the mechanism of acupoint sensitization has been predominantly understood as a peripheral manifestation driven by viscerosomatic reflexes, wherein internal pathology induces localized neurogenic inflammation, often mediated by mast cells, in the corresponding skin microenvironment[5–11]. In contrast, the findings by Tian et al.[2] advance this understanding by elucidating a top-down network where central psychological stress selectively recruits distinct sympathetic subpopulations (Pdyn$^+$) to remodel the local immune system. From this perspective, acupoints may be better understood as dynamic, state-dependent neuroimmune gateways, rather than fixed anatomical entities.

Neuroimmune microdomains: the anatomical substrate of disease specificity

The identification of Pdyn$^+$ sympathetic fibers forming dense plexuses in hairy skin, closely associated with eosinophil infiltration, offers a concrete anatomical and molecular substrate for this localized reactivity. These fibers form spatially restricted networks rather than uniform distributions, suggesting that stress-dependent activation is localized to specific and selectively responsive microdomains[2]. This pattern closely mirrors the discrete and condition-dependent nature of the sensitized acupoints.

These observations suggest that such neuroimmune microdomains may represent the biological basis of acupoint sensitization, where regional sympathetic–immune coupling—reflected in measurable features such as CCL11 profiles, eosinophil density, Adrb2 signaling activity, and local sympathetic fiber architecture—defines functional acupoint states. This localized architecture

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provides a logical framework for disease-specific sensitization. If distinct internal pathologies involve different central autonomic hubs, they may selectively recruit different sympathetic molecular subtypes. Such target-specific routing, a precise signaling pathway from central hubs to peripheral microdomains, may explain why different internal conditions manifest at different somatotopic coordinates[3–4,9–11].

Acupuncture as a context-sensitive modulator of functional neuroimmune networks

This framework also suggests that acupoint sensitization may serve as a strategic therapeutic window. Several studies indicate that targeting sensitized acupoints, where neuroimmune networks are primed by specific pathological signals, can elicit more efficient therapeutic responses than stimulating non-sensitized sites[9–11]. Sensitized acupoints act as selective gateways for peripheral neuromodulation.

Crucially, the efficacy of such modulation depends not only on the anatomical location but also on the precision of the stimulus design. Recent landmark studies by Liu et al.[12–13] and Dong et al.[14] demonstrated that distinct neural circuits are selectively recruited based on both the somatotopic site and stimulation intensity. The finding that optimal electroacupuncture intensities at the same site (eg, ST36) differ according to the target pathophysiology—for instance, 0.5 mA to mitigate systemic inflammation *via* the vagal–adrenal axis[12–13] as opposed to 3 mA to regulate gastric motility *via* the vago–vagal pathway[14]—further suggests that successful acupuncture depends on the precise alignment of the intervention with the physiological state and disease context.

The functional significance of this circuit-specific engagement is further supported by research on Parkinson disease models. By targeting the unique neuroimmune architecture of specific acupoint (eg, GB34) microdomains, peripheral mast cell-nerve crosstalk[15] is effectively transduced into the activation of distinct hypothalamic circuits[16], which in turn, alleviates Parkinsonian phenotypes. This indicates that acupuncture does not rely on diffuse neural activation; rather, it achieves an optimal efficacy when integrated with the molecular signature of the target site, precisely recalibrating the central regulatory systems. Ultimately, acupuncture can be defined as a context-sensitive neuromodulation technique in which stimulation parameters are calibrated for precise communication with upstream central autonomic networks.

Toward a bidirectional, circuit-based model of precision acupuncture

The findings of Tian et al.[2] support the view that brain–body communication is organized through anatomically discrete and functionally specialized circuits. Specifically, sympathetic neurons receive descending inputs from stress-related central hubs, including the paraventricular nucleus (PVN) and locus coeruleus (LC), forming a functional conduit that translates central stress perception into peripheral immune activation. Accumulating evidence indicates that peripheral interventions such as acupuncture can influence the central and systemic physiology through specific ascending pathways[12–16]. Integration of descending (pathological) and ascending (therapeutic) circuits creates a comprehensive bidirectional model of disease and therapy.

Several critical questions remain for future investigation. First, it is essential to verify whether stress-responsive areas exhibit sensitized acupoint characteristics and whether stimulating these specific sites is therapeutically beneficial. If they are confirmed, the subsequent research should determine whether this treatment directly modulates sympathetic activity or its downstream mediators (eg, the CCL11–CCR3 axis) in disease models.

The variability observed in acupuncture outcomes may stem from different internal states of patients. Future clinical trials should incorporate stress-level stratification and biomarker-based assessments (eg, circulating eosinophil levels or sympathetic tone) to identify specific responder populations. Calibrating acupuncture parameters, such as site, intensity, and frequency, to the pre-existing pathophysiological context of the target microdomain is essential for maximizing clinical efficacy through patient-centered optimization.

Beyond the stress–AD axis, another fundamental question is whether this neuroimmune model can be applied to other systemic conditions. For instance, whether different visceral inflammatory diseases activate distinct sympathetic subpopulations, thereby recruiting different immune effectors, such as mast cells or macrophages, to specific somatotopic coordinates. Defining how various disease states reshape local neuroimmune microdomains and how targeted interventions recalibrate these networks opens a promising path toward a universal framework for neuroimmune-targeted precision acupuncture.

Overall, the study by Tian et al.[2] advances our understanding of stress-induced inflammation and provides an essential biological link between neuroimmune interactions and acupoint sensitization. This perspective serves as a robust framework for future studies aimed at shifting acupuncture from a traditional point-based intervention to a circuit-based, context-sensitive neuromodulation strategy for improving systemic health.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

Hi-Joon Park wrote the original draft, and reviewed and edited the manuscript.

Ethical approval of studies and informed consent

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Data availability

No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Declaration of Generative AI in Scientific Writing

The author declares that no generative artificial intelligence (AI) technologies were used in the conception, drafting, or revision of this manuscript.

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