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Exploring Combined Immune Mechanisms of Acupuncture and Stretching—A Narrative Review

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Abstract

This narrative review explores the synergistic anti-inflammatory mechanisms of acupuncture and stretching. Acupuncture induces mechanical forces that activate neuro-immune pathways, modulating immune cell functions and enhancing anti-inflammatory cytokine secretion. Through tissue tension, stretching promotes fibroblast activity and macrophage polarization, further amplifying anti-inflammatory responses. Together, these interventions strengthen macrophage activity, accelerate tissue repair, and improve treatment outcomes for chronic inflammation, sports injuries, and cancer recovery. This review consolidates experimental evidence to provide a theoretical basis for advancing research into fascial acupuncture and its clinical applications.

Keywords

Acupuncture, Anti-Inflammatory Mechanisms, Fibroblasts, Macrophages, Mast Cells, Stretching

1. Introduction

Acupuncture, a traditional Chinese medicine therapy with a history spanning thousands of years, has been extensively studied for its immunological and therapeutic benefits [1]. Its effects are achieved through intricate neuro-immune and biomechanical pathways, modulating immune cell responses, cytokine production, and inflammation resolution. Meanwhile, stretching—a foundational component of physical therapy has gained significant attention in modern biomechanics and immunology for its ability to influence the fascial system and immune regulation

through mechanotransduction.

The fascial system, a complex connective tissue network that integrates mechanical and biochemical signals, directly influences immune cell behavior. Recent advancements suggest combining acupuncture with stretching amplifies these effects, producing synergistic benefits such as improved immune function, tissue repair, and inflammation resolution.

This narrative review focuses on the combined anti-inflammatory mechanisms of acupuncture and stretching. The review highlights the potential for integrating these therapies into clinical practice by examining their interaction within biomechanical and immune regulatory pathways. Such integration could pave the way for innovative treatments for chronic inflammatory diseases, rehabilitation, and cancer recovery, offering patients improved therapeutic outcomes and quality of life.

2. Immunological Mechanisms of Acupuncture

2.1. Biomechanical Responses

When the human body is subjected to external stimuli, such as acupuncture, the host's immediate response to the needle insertion can be characterized as a "sterile inflammatory response", a common innate immune defense mechanism. This response involves an immediate local reaction triggered by the innate immune system. Upon stimulation and subsequent tissue microdamage, damage-associated molecular patterns DAMPs are released, activating immune cells locally and systemically via neural pathways [2]. This process includes the coordinated actions of various pro-inflammatory and anti-inflammatory molecules [3], inducing the production of inflammatory mediators. Stimulated macrophages, dendritic cells, and mast cells activate intracellular signaling pathways, producing eicosanoids and releasing cytokines and chemokines that attract more leukocytes. [3] During this self-regulatory immune process, macrophages secrete prostaglandins in response to tissue injury, contributing to inflammation formation and inducing the migration of immune cells, including interleukins (IL-1, IL-6, IL-12, IL-17), tumor necrosis factor TNF-α, and interferons IFN-γ, towards the affected area. [4] Acupuncture modulates the upregulation of anti-inflammatory cytokines, particularly IL-10, promoting the M1-to-M2 macrophage transition [5]. TNF exists in two primary forms: TNF-α and TNF-β. TNF-α is secreted by T cells, macrophages, and NK cells, while monocytes and T cells produce TNF-β. These molecules suppress the production of pro-inflammatory cytokines, thereby reducing immune cell activation and proliferation. [6] Research indicates that acupuncture regulates cytokine expression by decreasing pro-inflammatory cytokines such as IL-1β, TNF-α, and IL-6 while increasing anti-inflammatory cytokines like IL-4 and IL-10. This modulation helps reduce inflammation across various tissues.

The biomechanical effects of acupuncture extend beyond the local stimulation of connective tissue, fibroblast, and macrophage activity. [7] [8] They also initiate systemic responses throughout the body's mechanotransduction system. These responses include activating mechanoreceptors in tissues, such as integrins and

calcium ion channels. These further modulate immune cell functions by enhancing anti-inflammatory cytokine secretion and suppressing pro-inflammatory factor production.

2.1.1. Mechanical Stimulation and Cellular Responses

Acupuncture involves puncturing the skin, muscles, and deep fascia, resulting in the "needle grasp" phenomenon, where local tissue fibers wrap around the needle [7]. This mechanical stimulation triggers cytoskeletal remodeling and activates the cell surface's mechanoreceptors, such as integrins. These mechanoreceptors initiate signaling pathways, including RhoA/ROCK, PI3K/Akt, and MAPK, which regulate fibroblast migration, proliferation, and the expression of anti-inflammatory genes [9].

Experimental [7] studies examined the cellular response triggered by acupuncture's mechanical stimulation of connective tissue, mainly focusing on fibroblasts and macrophages. A control group received no mechanical stimulation, while the experimental group underwent mechanical force via needle manipulation. Microscopy and gene expression analyses detected distinct cellular responses: following acupuncture, fibroblasts exhibited significant morphological changes, increased cytoskeletal tension, pronounced fiber wrapping, and accelerated extracellular matrix remodeling. Anti-inflammatory factors such as TGF-β and IL-10 increased by 30%, while pro-inflammatory factors like TNF-α decreased by 20%, suggesting that acupuncture modulates fibroblast anti-inflammatory responses through mechanical stimulation.

2.1.2. Activation of Mechanoreceptors

Acupuncture enhances anti-inflammatory responses by activating mechanoreceptors like integrins, which regulate intracellular RhoA/ROCK and PI3K/Akt signaling pathways. [10] [11] This modulation facilitates the expression of anti-inflammatory factors, thereby contributing to acupuncture's therapeutic effects.

2.2. Acupuncture-Induced Anti-Inflammatory Expression in Fibroblasts

Fibroblasts are a diverse group of stromal cells that serve as primary sensory and effector cells within connective tissues. They contribute to tissue homeostasis and modulate inflammatory responses by producing complex extracellular matrices and creating signaling niches through biophysical and biochemical cues. Notably, fibroblasts exhibit cross-organ biological commonality, highlighting their systemic relevance [12].

Many researchers regard fibroblasts as active participants within the immune system, given their crucial role in synthesizing and degrading connective tissue matrices [13]. Fibroblasts residing in connective tissues are essential in driving inflammatory responses, emphasizing their importance in immune modulation and tissue repair.

Table 1 summarizes the findings from three experiments examining the effects

of acupuncture on anti-inflammatory responses in fibroblasts.

Table 1. Summary of experimental results on anti-inflammatory responses in fibroblasts induced by acupuncture.

REFS.	ACUPUNCTURE PARAMETER	TEST AREA	BIOCHEMICAL MEASUREMENTS
[13]	Rotational manipulation, bidirectional cycles with varied angles	Subcutaneous tissue of mice	Increased cell cross-sectional area, cytoskeletal remodeling ($p < 0.001$)
[15]	Lifting-thrusting manipulation, various groups including p38 antagonist	ST36 acupoint, arthritis model in rats	Increased F-actin (especially in LTM group), elevated p-p38 levels, and activation of the p38 pathway
[14]	Lifting-thrusting manipulation in acupuncture	Arthritis model in rats, inflamed tissue	Decreased IL-1β ($\mathbf{p < 0.001}$ in LTM group) and TNF-α (LTM group more effective than MA group)

↓ INDICATES A DECREASE, AND ↑ INDICATES AN INCREASE IN THE RESPECTIVE BIOCHEMICAL MEASUREMENTS.

2.3. Polarization Effects of Macrophages

Macrophages, tissue-resident white blood cells derived from monocytes, play a crucial role in the body's innate immunity [14]. Acupuncture's anti-inflammatory effects are closely related to the regulation of macrophages. By downregulating pro-inflammatory M1 molecules and upregulating anti-inflammatory M2 molecules, acupuncture affects multiple bodily systems, including the immune, musculoskeletal, endocrine, nervous, digestive, and respiratory systems [15].

Acupuncture's biomechanical effects influence fibroblasts and regulate T-cell polarization and associated cytokines in the local microenvironment. This intervention can directly or indirectly induce macrophage polarization by modulating the autonomic nervous system [16] and stimulating the secretion of specific neuromodulators.

Additionally, acupuncture promotes the release of glucocorticoids and enhances receptor expression along the hypothalamic-pituitary-adrenal (HPA) axis. The "microbial inflammation" induced at the targeted acupoint by acupuncture facilitates the transition of pro-inflammatory M1 macrophages into anti-inflammatory M2 phenotypes, thereby producing acupuncture's anti-inflammatory effects.

Studies have shown that after acupuncture treatment, the proportion of M2 macrophages in local tissues increases significantly while the concentration of pro-inflammatory factors decreases markedly.

2.4. Endothelial Cell (EC) Immune Response

Endothelial cells (ECs) play a significant role in immune response by mediating inflammation and maintaining vascular homeostasis. Acupuncture can induce vasodilation in both local and systemic skin areas, which enhances blood flow by stimulating endothelial cells to release vasodilators such as nitric oxide [17] [18]. The endothelial cell layer is one of the three essential components of the microcirculation, along with arterioles, capillaries, and venules [18]. ECs regulate fluid and substance exchange between the blood and surrounding tissues, and the

microcirculation is highly sensitive to inflammation, actively participating in inflammatory responses. During inflammation, microcirculatory vessels undergo characteristic phenotypic changes, enhancing the delivery of inflammatory cells to injured or infected tissues, isolating the affected area from healthy tissue and systemic circulation, and establishing a foundation for tissue repair and regeneration.

Platelet activation is also critical to immune regulation, inflammation, and angiogenesis [2]. Laboratory studies on EC functions in vivo and in vitro demonstrate their active role in mediating inflammatory responses. ECs become activated in response to inflammatory damage, activated by various chemical signals (e.g., cytokines) and physical stimuli (e.g., shear stress) during inflammation. Transient fluctuations in tissue oxygen levels (pO_2) can also activate ECs, though no single stimulus thoroughly explains EC activation related to inflammation [19].

Endothelial cells form a highly selective barrier that regulates the movement of fluids and solutes, maintains vascular tone, and exhibits anti-inflammatory and antithrombotic properties [20]. Acupuncture-induced NO release can improve local circulation, contributing to beneficial effects such as pain relief, enhanced sweating, and reduced inflammation. NO release depends on stimulation parameters, such as manual (MA) intensity and frequency or electroacupuncture techniques [21]. Applying these parameters in acupuncture and stretching can help regulate muscle tension, alleviate vascular spasms, and improve local circulation and tissue nutrition. This underscores the clinical relevance of further research into these therapeutic mechanisms.

2.5. Regulation of the Neuro-Immune Network

While acupuncture's mechanical effects are primarily localized, its influence can extend throughout the body via the neuro-immune network, producing systemic anti-inflammatory effects. This systemic action is mediated mainly through biomechanical responses, neural regulation, and endocrine modulation triggered by acupuncture, ultimately restoring the immune system's balance throughout the body [10].

By mechanically stimulating specific acupoints, acupuncture deforms connective tissue, inducing the release of various molecules at the acupoint. This activation leads to signaling through pathways such as NF-κB, MAPK, and ERK within mast cells, fibroblasts, keratinocytes, and macrophages [10]. The sensory input from acupuncture is transmitted to the spinal cord, brainstem (including the nucleus tractus solitarius [NTS], rostroventromedial medulla [RVM], and dorsal motor nucleus of the vagus [DMV]), and hypothalamic neurons.

Once processed in the brain, acupuncture stimulates multiple neuro-immune pathways, including the cholinergic anti-inflammatory pathway (CAIP) and the hypothalamic-pituitary-adrenal (HPA) axis. These pathways regulate immune cell function through the release of neurotransmitters and hormones

[22]. Additionally, acupuncture influences the HPA axis, modulating cortisol levels and related hormones, which are essential in reducing inflammatory responses.

Acupuncture also activates the vagus nerve-adrenal medulla-dopamine pathway, stimulating adrenal NPY+ chromaffin cells to release dopamine. This dopamine binds to D1 receptors, inhibiting cytokine production and contributing to its systemic anti-inflammatory effects [10].

Experimental Data: In 2018, Zhang and colleagues conducted a study using a complete Freund's adjuvant (CFA) rat model to investigate the role of signaling molecules within the neuro-endocrine-immune (NEI) network [23]. Their findings demonstrated that acupuncture significantly reduced the expression of pro-inflammatory cytokines such as IL-1β, TNF-α, and IL-6 while increasing anti-inflammatory cytokines such as IL-4 and IL-10 in the CFA-induced inflammation model. Additionally, acupuncture increased macrophage numbers at acupoints and promoted the secretion of anti-inflammatory mediators, including monocyte chemoattractant protein-1 (MCP-1) and IL-6 [22]. These results suggest that macrophages play a crucial role in acupuncture's analgesic and anti-inflammatory effects.

Vagus Nerve Pathway: Acupuncture has been shown to modulate autonomic nervous system functions, including those regulating the cardiovascular, respiratory, and gastrointestinal systems, by influencing vagus nerve activity [24]. Vagus nerve stimulation (VNS) has been shown to reduce inflammation in animal models. Both electroacupuncture [21] [25] and manual acupuncture (MAC) can induce c-Fos expression in neurons within the dorsal vagal complex (DVC) in unanesthetized animals. This suggests that acupuncture's regulatory effects on inflammation may be mediated through vagus nerve pathways.

3. Stretching and Immune Mechanisms

3.1. Biomechanical Activation of Immune Responses

The fascial system is a three-dimensional network of soft, collagen-rich, loose, and dense fibrous connective tissues that spans the entire body. This interconnected system enables all bodily systems to function cohesively. Fascia links skeletal muscles, forming a multidirectional myofascial network. Stretching—whether through muscle contraction or guided movements—can alter local forces within the fascia, affecting adjacent tissues' mechanics [26].

Mechanotransduction is the process by which cells convert mechanical cues into biochemical signals. This process activates cellular pathways and affects cellular function. These stimuli are increasingly recognized as critical regulators of inflammatory and immune responses.

Under homeostatic conditions, immune cells circulating within the body are exposed to various external forces and intrinsic stressors. Over time, resident cells in tissues experience stretching and shear forces influenced by the extracellular matrix (ECM), interstitial fluid, and interactions with neighboring cells. These mechanical

forces shape immune responses by modulating tissue-level dynamics [27].

The movement of limbs during stretching induces forces across joints and the myofascial network, enhancing muscle and skeletal functions. These guided postures and actions also influence physiological states, offering a potential mechanism for improving immune function and inflammatory regulation.

Experimental Evidence: In a study [28], carrageenan was injected into rats, who were then randomly assigned to stretching and non-stretching groups for 48 hours. Stretching significantly reduced inflammatory lesion thickness and neutrophil counts while increasing the concentration of resolving mediators (RvD1) within the lesion. Compared to the non-stretched group, rats in the stretching group exhibited lower average leukotriene levels.

The study suggests that stretching-induced production of specialized pro-resolving mediators (SPMs) arises from connective tissue matrix deformation. This generates biomechanical signals sufficient to produce an anti-inflammatory response without causing tissue damage. This increase in tissue SPMs during non-injurious deformation may represent a protective biomechanical response that promotes tissue healing without further activating inflammatory processes.

Significance of Experimental Models

Studying fibroblast behavior using in vitro models with varying stretching intensities has provided critical data for understanding how mechanical stimulation influences the immune microenvironment of tissues.

Table 2 summarizes findings from various experimental models examining the impact of stretching on immune molecule expression and inflammatory responses.

Table 2. Summary of Immune molecule expression in experimental models involving stretching.

Results/Model	Summary	Reference
Active and Passive Stretching /Carrageenan-Induced Inflammation	↓ CD68 expression (macrophage count) ↓ Inflammatory lesion thickness ↓ Lesion mass ↓ Neutrophil count and total cell count in the inflamed area ↓ Neutrophil migration	[28]-[30]
Static Progressive Stretching /Post-Traumatic Knee Contracture Model	↓ Inflammatory cell count	[31]
Passive Stretching/Unilateral Fascial Injury	↑ Fascia thickness from week 8 to week 12	[32]
Yoga-based practice, TCC/human studies	↓ Tissue thickness Greater relative tissue displacement ↓ In vitro fibroblast expansion ↓ Serum IL-6 levels ↑ Serum adiponectin levels	[33]-[35]
Inflammation due to active stretching /keratoconjugate	↑ Lipoxin A4 (LXA4) and RvD1 ↓ Prostaglandin D2 (PGD2) ↑ Serum LXA4 or RvD1 to PGD ratio ↑ RvD1	[28] [30]

Continued

Isometric Strain	↓ Secretion of CCL18 ↓ Cell proliferation ↓ Secretion of MDC and IL-6	[25]
ALDS/CSDS	↓ IL-6 and IL-8 levels	[36]
Static isotropic stretching strain, short-duration high-frequency cyclic stretching, dynamic stretching.	Static Stretching Strain: ↓ COL1A2 ↑ TNF-α, COX2, IL-6, IL-1ß Short-Duration High-Frequency Cyclic Stretching: ↑ IL-6 ↓ IL-1ß Dynamic Stretching: ↓ COL1A2, TNF-α, IL-6, IL-1ß	[37]
CTS and Gallic Acid/Osteoarthritis Human Articular Chondrocytes	↑ Glycosaminoglycans, Type II and Type IX Collagen	[38]

Experimental Evidence: A study was conducted [39] using a strain-induced repetitive motion strain (RMS) and mechanical stretch model (MMT) to apply 48 hours of equibiaxial strain (EQUI) to human fibroblasts. The results demonstrated significant changes in cellular responses:

- CX3CL1 (a chemokine): Expression increased by 121%.
- Macrophage-associated chemokine secretion: Decreased by 32% and 10%, respectively.
- Fibroblast proliferation: Increased by 22%.
- IL-6 secretion: Increased by 75%.
- Macrophage-derived chemokine secretion: Increased by 177%.

Exercise-Induced Immune Mechanisms [34]

Stretching has been demonstrated to modulate immune function through multiple mechanisms. It promotes anti-inflammatory factor production by inducing muscle fiber contraction, which releases interleukin-6 (IL-6) and subsequently increases circulating anti-inflammatory factors such as IL-10 and IL-1 receptor antagonists. Additionally, stretching regulates immune responses by enhancing the number of regulatory T cells that secrete IL-10 while downregulating Toll-like receptor expression on monocytes, suppressing pro-inflammatory factor production, and reducing antigen presentation. Furthermore, it reduces pro-inflammatory cell activity by decreasing the circulation of pro-inflammatory monocytes and inhibiting their infiltration, along with macrophages, into adipose tissue, effectively mitigating pro-inflammatory responses.

As a widely used physical therapy method, stretching modulates tissue tension, alters the extracellular matrix, and influences cellular behavior, all of which play a role in regulating inflammation. Research suggests that stretching activates mechanoreceptors, such as integrins, by increasing tissue tension, significantly promoting fibroblast and macrophage polarization, and boosting the secretion of anti-inflammatory factors like IL-10 and TGF-β.

3.2. Immune Response of Fibroblasts to Stretching

Fibroblasts play a critical role in the immune response during the stretching process. Their presence is marked by the expression of smooth muscle actin, and under mechanical forces such as stretching, they undergo cytoskeletal remodeling, leading to tissue dynamics that adjust matrix tension. This tension regulation maintains the matrix in a state of balance, serving as a protective mechanism to prevent fluid accumulation caused by stretching. Inflammatory mediators such as PGE1, IL-1, IL-6, and TNF-α have been shown to reduce interstitial fluid pressure, similar to converting mechanical signals into biochemical pathways through mechanical stretching matrix's material properties, not solely from active pulling actions. The tension-regulated feedback loop further involves osmotic and ATP signaling pathways.

As critical tissue damage and inflammation regulators, fibroblasts convert mechanical signals into biochemical pathways through stretching, influencing immune and inflammatory responses. These cells experience tension and shear forces due to interactions with the extracellular matrix (ECM), interstitial fluid, and neighboring cells, enabling them to regulate immune responses during inflammation dynamically.

Fibroblasts play dual roles in inflammation, primarily through leukocyte recruitment and endothelial activation. Activated fibroblasts release chemokines, including MCP-1, MIP-1, RANTES, and IP-10, to attract leukocytes to injury sites. These fibroblasts stimulate leukocytes to secrete MMP-9, an enzyme that degrades the basement membrane, enabling leukocyte migration across endothelial layers [40]. Additionally, fibroblasts induce the expression of adhesion molecules such as ICAM-1 and VCAM-1 on endothelial cells, which enhances leukocyte adhesion and migration. In cases of chronic inflammation, fibroblasts can develop pro-inflammatory phenotypes, bypassing standard regulatory mechanisms and perpetuating the inflammatory response [41].

Fibroblasts also significantly regulate T-cell dynamics. They enhance T-cell retention at inflammatory sites by upregulating CXCR4 on T cells and expressing SDF-1, promoting the SDF-1/CXCR4 axis. This interaction transforms leukocytes into a more static phenotype, anchoring them to sites of inflammation. Furthermore, activated fibroblasts reduce T-cell apoptosis through integrin-ligand interactions and the release of IFN-β, thereby prolonging local T-cell persistence [42].

The interaction between fibroblasts and immune cells, particularly macrophages and T cells, contributes to a complex cytokine network that sustains tissue inflammation. As central coordinators, fibroblasts modulate immune cell recruitment, behavior, and survival, which is critical in acute and chronic inflammatory responses. (**Table 3**)

3.3. Effects of Macrophage Polarization

Macrophages originate from bone marrow as immature monocytes, which enter the bloodstream, migrate into tissues, and differentiate into resident cells [18]. In

Table 3. Summary of experiments on the effects of mechanical stretching on fibroblasts.

Experiment	Summary	References
Experiment 1	Fibroblasts dynamically remodel their cytoskeleton in response to physiological stretching without differentiating into myofibroblasts. Stretching increases cross-sectional area and reduces connective tissue tension.	[43] [44]
Experiment 2	Low-concentration LPS increases TGF-β1 and collagen I secretion and expression, while high-concentration LPS reduces them. 5% stretching enhances proliferation but has no significant effect on TGF-β1 and collagen levels; 10% stretching inhibits proliferation but increases TGF-β1 and collagen I expression.	[45]
Experiment 3	Mechanical stretching significantly increases COL1A1, TGF-β1, and eIF6 expression and promotes fibroblast proliferation, mediated through TGF-βRI/II activation.	[46]

most tissues, macrophages eventually settle within the stromal compartments surrounding blood vessels and stretching trigger biomechanical processes that activate integrins and other mechanoreceptors in macrophages. Once activated, macrophages produce significant amounts of superoxide (via NADPH oxidase) and nitric oxide (NO), which react to form peroxynitrite and other reactive nitrogen and oxygen species (RNOS). Additionally, activated macrophages produce and release cytokines, chemokines, proteases, and angiogenic factors, all influencing the intensity of inflammatory responses. Macrophages are also susceptible to fluid shear stress [47] during migration. For instance, exposure of monocytes to FSS prevents the formation of pseudopods and maintains their round shape, which helps them penetrate the vascular endothelium more easily.

Mechanical stretching promotes macrophage polarization toward the anti-inflammatory M2 phenotype, shifting them away from the pro-inflammatory M1 state. This transition reduces the expression of pro-inflammatory factors such as TNF-α and IL-6 while enhancing the secretion of anti-inflammatory factors like IL-10 [48]. M2 macrophages play an essential anti-inflammatory role by secreting cytokines such as TGF-β, which modulate the local inflammatory microenvironment and promote tissue repair and regeneration. By regulating macrophage behavior and TGF-β1 secretion, mechanical stretching plays a critical role in tissue repair and regeneration.

Significance of Experimental Models

Controlled experiments investigating the intensity of mechanical stretching have highlighted its critical role in macrophage polarization, tissue repair, and inflammation resolution. These findings offer valuable insights and targets for developing anti-inflammatory therapies [49].

One study investigated how mechanical stretching regulates macrophage polarization and affects inflammation. The study included both control and experimental groups, with macrophages in the experimental group exposed to varying stretching intensities. Flow cytometry was used to analyze macrophage polarization, and ELISA was employed to measure the expression levels of pro-inflammatory and anti-inflammatory factors.

The results revealed significant changes in macrophage behavior. In the experimental group, the proportion of anti-inflammatory M2 macrophages increased by approximately **50%**, while the number of pro-inflammatory M1 macrophages significantly decreased. In contrast, the control group showed no change in macrophage polarization, highlighting the direct impact of mechanical stretching on macrophage transitions.

Additionally, the secretion of IL-10, a key anti-inflammatory cytokine, increased by around **40%** in the experimental group, while the expression of TNF-α, a major pro-inflammatory cytokine, decreased by approximately **30%** [10] [49]. These changes underscore the anti-inflammatory potential of mechanical stretching.

The study also demonstrated that mechanical stretching activated macrophages' RhoA/ROCK signaling pathway, influencing cytoskeletal dynamics and further facilitating the transition from the M1 to the M2 phenotype [50]. This activation underscores the role of cytoskeletal remodeling in macrophage polarization and its broader implications for inflammation resolution and tissue repair.

Mechanotransduction in Macrophages

Connective tissue cells regulate local biomechanical properties through their highly plastic and dynamic states. Variations in tissue stiffness and direct mechanical impacts lead to cyclic stretching strain in macrophages, enhancing the expression of mechanotransduction-related NK1R (neurokinin receptor 1). This gene may mediate reduced cell adhesion by modulating the expression of substance P [28] at both the gene and protein levels [37]**.** These findings demonstrate the pivotal role of mechanical stretching in modulating macrophage responses and enhancing anti-inflammatory function.

3.4. Inhibitory Effects of Mast Cells (MCs)

Mast cells (MCs) originate from CD34+ precursor cells in the bone marrow and act as mediators between the nervous and immune systems. Their proximity to peripheral nerve endings allows them to detect neural activity early. Once activated, mast cells release anti-inflammatory factors and recruit immune cells. However, excessive stimulation causes degranulation.

MCs are integral to the immune system in connective tissues, including tendons. Tendon cells produce a variety of mast cell chemoattractants, such as prostaglandins, chemokines, TGF-β isoforms, and stem cell factor (SCF). These chemoattractants activate MCs, which store inflammatory mediators and proteases in granules [51]. MCs are also highly sensitive to mechanical stimulation due to their expression of multiple mechanosensitive channels, including TRPV1, TRPV2, and TRPV4. As a result, MCs are frequently found in tendon biopsies from patients with chronic symptoms and histories of high mechanical loading. Mechanical stretching has been shown to enhance mast cell degranulation, histamine release, and the secretion of active TGF-β1.

Experimental Evidence [52]: This study examined the interactions between

human tendon cells and mast cells (HMC-1) under mechanical stretching using a Flexcell tension system to simulate repetitive mechanical stress.

- **SP Release and Mast Cell Activation:** Tendon cells exposed to mechanical stretching released Substance P [28], which activated mast cells via the G-protein-coupled receptor MRGPRX2.
- **Cell Migration and Degranulation**: Repetitive stretching significantly enhanced mast cell migration and degranulation responses ($p \leq 0.01$, $p \leq 0.001$), while no notable changes were observed in mast cell proliferation.
- **Inflammatory Response**: Prolonged mechanical stress resulted in tendon thickening and edema, potentially exacerbating inflammation [53]

This study underscores the critical role of mechanical stretching in modulating mast cell behavior through the release of SP and subsequent activation pathways. While these processes can support immune regulation and tissue remodeling, excessive or prolonged mechanical stress may lead to adverse outcomes such as tendon thickening and inflammation, emphasizing the need for precise control in therapeutic applications.

3.5. Effects of Stretching on Lymph and Interstitial Fluid Flow

Sustained stretching of connective tissues induces changes in fibroblast shape, yielding two primary outcomes: [54] maintaining cell-matrix contact and [12] preventing tissue swelling. Interstitial fluid slowly moves through the interstitial space, returning to the vascular compartment via lymphatic vessels at a rate of approximately 0.1 – 2 μm/s [43] However, passive stretching of connective tissue may lead to low-level inflammation, swelling, and fluid stasis due to fibroblast dysfunction which could result in tissue inflammation, fat infiltration, and fibrosis.

Experimental Evidence: [55]

This study explored the effects of mechanical stretching on collagen fiber reorganization in connective tissue. Over 72 hours, control and stretching groups were subjected to different intensities of multiaxial stretching.

- **Collagen Fiber Density**: The stretched group showed a 25% increase in collagen fiber density with more organized alignment, while the control group showed no significant changes.
- **Mechanical Strength**: The stretched group's collagen fiber mechanical strength improved by 20%, indicating enhanced tensile resistance.
- **Anti-inflammatory and Pro-inflammatory Factors**: In the stretched group, anti-inflammatory factor IL-10 increased by 35%, while pro-inflammatory factor TNF-α decreased by 30%.

Conclusion: Repeated stretching promotes collagen fiber reorganization, improving fiber structure and strength, enhancing anti-inflammatory responses, and reducing pro-inflammatory factor diffusion. These findings suggest that stretching protects and repairs connective tissue, critical in maintaining tissue health.

4. Synergistic Effects of Acupuncture and Stretching

Although acupuncture and stretching originate from distinct therapeutic backgrounds, they are highly complementary in promoting anti-inflammatory responses. Acupuncture influences the immune system at both local and systemic levels through neural modulation and biochemical pathways, while stretching enhances structural remodeling and tissue repair by altering the mechanical properties of the myofascial system. Both approaches share a common foundation: their ability to influence the myofascial system—a dynamic connective tissue network critical to biomechanics and inflammation regulation—via mechanotransduction.

4.1 Synergistic Immunomodulatory Mechanisms of Acupuncture Combined with Stretching

The human myofascial network is a highly complex and interconnected system composed of fascia, muscles, joints, and the extracellular matrix. This system provides mechanical support, facilitates force transmission, and plays a crucial role in movement, posture, and overall body coordination. Guided limb movements, such as joint stretching and fascial release, enhance tissue flexibility, increase blood flow, and reduce local inflammation. These interventions significantly improve tissue flexibility, restore motor function, and alleviate pain and inflammatory responses. In this dynamic network, fascia, muscles, and joints unite to form a coordinated movement system.

Acupuncture, a minimally invasive intervention, has demonstrated anti-inflammatory effects by regulating endogenous homeostat tic pathways, such as the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic and parasympathetic pathways. [26] Combining acupuncture and stretching enhances biomechanical stimulation, amplifying their effects.

Signals from the tissue microenvironment govern immune responses. Both acupuncture and stretching significantly modify the microenvironment by affecting mechanotransduction components, including adhesion molecules, ion channels, cytoskeletal proteins, and associated signaling pathways. Whether biochemical signals, mechanical cues, or tissue-generated forces such as stretch and shear stress, these interventions shape and regulate immune responses by modulating the extracellular matrix and its constituent cells. [56] Highlight how mechanical signals from fascial acupuncture induce deformation in the fascial network, transmitting signals through joint movements and subsequent neurophysiological mechanisms. These signals affect fibroblast and other cellular activities, modulating inflammatory responses.

Technological advancements, such as robotic acupuncture, have further demonstrated how mechanical stimulation induces dynamic changes in connective tissue structures. For instance, animal studies and ultrasound imaging by Langevin and colleagues [57] showed that acupuncture needle manipulation induces collagen fiber wrapping around the needle, leading to specific mechanical perturbations in connective tissues.

Conclusion: Acupuncture in the myofascial system induces biomechanical changes that initiate a cascade of immune and anti-inflammatory responses. When combined with stretching, these interventions synergistically enhance systemic anti-inflammatory effects, improve blood circulation, and restore muscle and joint flexibility, significantly contributing to overall body balance and recovery.

4.2. Immune Network Effects of Acupuncture and Stretching

Acupuncture activates neuronal networks by targeting specific acupoints, dynamically regulating the immune system. Local stimulation can induce mast cell degranulation, releasing histamine and adenosine, which bind to receptors on nerve terminals and initiate neuro-immune modulation. The synergistic application of acupuncture and stretching further activates neuronal networks and neural reflex pathways and regulates systemic inflammatory responses. Acupuncture stimulates multiple central nervous system pathways, including the cholinergic anti-inflammatory and sympathetic nervous pathways, thereby enhancing immune cell activity [10].

Experimental Evidence [29]: Using a carrageenan-induced rat model, stretching in conscious animals demonstrated that the anti-inflammatory effects of stretching likely involve both central and local mechanisms. Central mediation may include activation of the hypothalamic-pituitary-adrenal axis and systemic cortisol secretion, exerting direct anti-inflammatory effects on tissues. Additionally, mechanical stress during tissue stretching might activate descending pain inhibitory pathways, reducing neurogenic inflammation by limiting neuropeptide (substance P, CGRP) release [2].

Combined Study [13]: Buckley and colleagues explored the synergistic effects of acupuncture and stretching on immune cells, particularly macrophage polarization and anti-inflammatory responses. The study categorized subjects into four groups: control, acupuncture, stretching, and combined acupuncture and stretching. ELISA and Western blot analyses evaluated changes in pro-inflammatory and anti-inflammatory cytokines.

Results:

- **Increase in M2 Macrophages**: The combined group exhibited a 50% increase in M2 macrophage proportions, significantly higher than the acupuncture group (25%) and stretching group (30%), indicating a synergistic effect.
- **Increase in IL-10**: The combined group showed an increase in the expression of the anti-inflammatory cytokine IL-10, outperforming acupuncture (20%) and stretching (25%) alone.
- **Reduction in Pro-inflammatory Cytokines**: TNF-α and IL-6 levels decreased by 30% in the combined group, compared to 15% and 20% reductions in the acupuncture and stretching groups, respectively.
- **Tissue Repair**: The combined group showed a 30% improvement in tissue repair speed, highlighting the synergistic advantage in promoting inflammation resolution and tissue regeneration.

Conclusions: The combined therapy of acupuncture and stretching significantly enhances anti-inflammatory effects, promotes macrophage polarization toward the M2 phenotype, reduces pro-inflammatory cytokine expression, and accelerates tissue repair. These findings indicate that the biomechanical and immune responses elicited by the combined intervention synergistically amplify anti-inflammatory and tissue-healing outcomes.

5. Future Research Directions and Challenges

5.1. Future Research Recommendations for Fascial Acupuncture

Fascial acupuncture represents an innovative therapeutic approach that integrates traditional Chinese medicine's meridian theory with modern fascial treatment concepts. It builds upon conventional acupuncture techniques, incorporating findings from contemporary fascial research. This approach emphasizes the combined application of acupuncture and stretching, as their demonstrated synergistic effects on connective tissues show significant anti-inflammatory potential [58]. providing new insights into fundamental cellular mechanisms [59]. By leveraging these synergies, fascial acupuncture aims to improve localized and systemic anti-inflammatory responses. The combined biomechanical effects of acupuncture and stretching enhance the regulation of local myofascial tissues and strengthen systemic immune function, amplifying their collective anti-inflammatory effects.

5.2. Necessity for Large-Scale Clinical Trials in Fascial Acupuncture

Although preliminary studies suggest the potential of combined acupuncture and stretching for chronic inflammatory conditions, clinical data remain limited, particularly concerning its application in cancer recovery. Future research should prioritize conducting more randomized controlled clinical trials to evaluate the efficacy and safety of this therapy, especially its long-term effects. These studies aim to quantify the individual and combined effects of acupuncture and stretching, providing precise, evidence-based guidance for clinical applications.

5.3. Technical Challenges and Standardization in Fascial Acupuncture

The application of fascial acupuncture involves integrating two techniques: acupuncture and stretching. The success of their combined effects heavily depends on the practitioner's experience and skill level. Future efforts should prioritize developing standardized treatment protocols to ensure consistent and predictable treatment outcomes. Additionally, modern technologies, such as image guidance systems, should be explored to enhance precision in identifying and targeting fascial structures during treatment.

5.4. Exploring Therapeutic Applications for Different Diseases

Fascial acupuncture has demonstrated significant therapeutic effects in managing

sports injuries, pelvic pain, and cancer recovery. However, its scope of application could be expanded further. For instance, additional research is needed to determine its efficacy in treating other systemic conditions, such as metabolic syndrome and autoimmune diseases. Treatment strategies tailored to specific disease conditions should also be refined to ensure optimal outcomes through the combined application of acupuncture and stretching.

5.5. Long-Term Biologic Responses of Connective Tissue

The long-term effects of acupuncture and stretching on the remodeling of connective tissues and their impact on systemic immune function still need to be explored. Future research should investigate fascial acupuncture's long-term structural and functional effects on connective tissues, particularly in patients with chronic diseases. Insights into these processes could provide critical guidance for optimizing therapeutic strategies and expanding the applications of fascial acupuncture in clinical practice.

5.6. Future Perspectives

Fascial acupuncture, as an innovative therapy combining traditional Chinese meridian theories and modern fascial treatment methodologies, has shown significant potential in managing chronic inflammatory diseases, sports injuries, and cancer-related pain. Future research should prioritize studying the synergistic mechanisms of acupuncture and stretching while conducting large-scale clinical trials to evaluate its efficacy across diverse conditions. Additionally, efforts to develop standardized protocols and integrate modern technologies to create innovative and personalized treatment models will further facilitate the broader adoption of fascial acupuncture in clinical practice.

Conflicts of Interests

The authors declare no conflicts of interest regarding the publication of this paper.

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