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Exploring the Connection Between Phlegm–Stasis Interaction and Liquid–Solid Interface Inflammation in Autoimmune Diseases

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Abstract: ***In autoimmune diseases, immune responses at the liquid–solid interface play a pivotal role in the persistence of inflammation and the progression of tissue damage. From the perspective of Traditional Chinese Medicine (TCM), the pathological concept of "Phlegm–Blood Stasis Interaction" reflects the tendency of viscous pathogenic factors to accumulate and obstruct at tissue interfaces, which shows a high degree of correspondence with the interface inflammation mechanism described in modern medicine. This convergence highlights the interface as a critical site where pathological mediators drive disease chronicity and organ injury. The present study integrates insights from both TCM and modern immunopathology to systematically analyze the correlations in etiology, lesion localization, material characteristics, and clinical manifestations. Furthermore, we review the progress of Chinese herbal medicine interventions targeting interface inflammation, with particular attention to their regulatory effects on immune–inflammatory processes. These findings not only provide theoretical support for the involvement of TCM in autoimmune disease management but also propose practical pathways for innovative integrative therapeutic strategies.***

Keywords: Liquid–Solid Interface, Phlegm–Blood Stasis Syndrome, Autoimmune Diseases**.**

1. Introduction

Autoimmune diseases (ADs) are chronic disorders characterized by a breakdown of immune tolerance, whereby the immune system aberrantly attacks self-tissues. Representative conditions include rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) [1]. These diseases are typically marked by recurrent inflammation, progressive tissue injury, and complex clinical manifestations, making them a major burden for patients and healthcare systems worldwide. Despite extensive advances in immunopathology, current therapeutic approaches remain limited by incomplete efficacy, adverse effects, and disease relapse, highlighting the need for novel mechanistic insights and integrative intervention strategies.

Recent studies in immunology have identified the liquid–solid interface as a crucial site mediating persistent inflammation and tissue damage in ADs. This interface involves immune recognition, adhesion, and activation processes occurring between liquid environments (e.g., synovial fluid, plasma) and solid tissues (e.g., synovial cells, vascular endothelium), and is orchestrated by multiple inflammatory mediators and adhesion molecules [2]. Dysregulated immune responses at this interface contribute to chronic inflammation and sustained pathology, positioning it as a potential therapeutic target.

In parallel, clinical observations in traditional Chinese medicine (TCM) have long noted that ADs present with symptoms such as joint redness, swelling, heat, pain, limb heaviness, numbness, and protracted disease courses. Within TCM theory, the classical concept of "phlegm-dampness obstructing the collaterals" has evolved into the more refined framework of "phlegm–blood stasis interaction." This pathological construct emphasizes the mutual congealing of turbid phlegm and blood stasis, obstructing the meridians, impairing the flow of qi and blood, and eventually transforming into heat to form the syndrome of "phlegm–heat and blood stasis obstruction." The traditional description — "dampness initiates disease, dampness stagnates to form phlegm, phlegm combines with stasis, stasis generates heat, and pathogenic factors interweave to cause obstruction" — bears striking resemblance to the modern notion of liquid–solid interface reactions in terms of medium properties, disease localization, and persistence of inflammation [3].

Although parallels between interface immunology and TCM pathogenesis have been conceptually suggested, a systematic comparative framework remains underdeveloped. In particular, the correspondence between liquid–solid interface responses and the theory of phlegm–blood stasis interaction has not been fully elucidated in relation to etiology, pathological progression, and clinical manifestations. Addressing this gap is essential for advancing integrative pathogenesis models and for guiding innovative therapeutic approaches that combine modern immunological understanding with TCM-based strategies.

Therefore, this review aims to systematically summarize the mechanistic role of liquid–solid interface responses in autoimmune diseases, and conduct a comparative analysis with the TCM theory of phlegm–blood stasis interaction. By constructing an interdisciplinary explanatory framework, this article seeks to enrich the perspectives and methodologies of integrative medicine research, and to provide theoretical grounding and practical insights for TCM interventions in autoimmune diseases.

2. Overview of Liquid–Solid Interface Immune Responses

2.1 Concept and Connotation

The concept of the liquid–solid interface immune response has emerged as a novel perspective for understanding chronic inflammation in autoimmune diseases. It refers to the dynamic processes of immune recognition, adhesion, activation, and signal transduction that occur between liquid environments (such as synovial fluid, plasma, and interstitial fluid) and solid tissue surfaces (including synovial cells, endothelial cells, and cartilage). Within this microenvironment, diverse mediators—ranging from immune cells and cytokines to the complement system and extracellular vesicles—directly act on tissue cells at the interface. Such interactions can drive either inflammatory injury or reparative remodeling processes.

Mechanistically, the occurrence and intensity of interface responses are governed by two interdependent elements: (i) the composition and concentration of inflammatory mediators within the liquid phase, exemplified by interleukin (IL)-1β, tumor necrosis factor (TNF)-α, and IL-6; and (ii) the expression patterns of receptors and adhesion molecules on solid-phase surfaces, such as vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and major histocompatibility complex class II (MHC-II) on fibroblast-like synoviocytes (FLS). The interplay between these components determines whether immune cells become activated at the interface, whether chemotactic signaling is induced, and whether self-perpetuating inflammatory cascades are established [4–6]. This framework provides a mechanistic bridge linking soluble inflammatory mediators with tissue-level pathology.

2.2 Typical Manifestations in Autoimmune Diseases

Evidence from various autoimmune diseases underscores the importance of liquid–solid interface immune responses as a central driver of persistent inflammation and progressive tissue injury. Among these, rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) represent prototypical conditions in which interface-mediated mechanisms are particularly well characterized.

In RA, synovial fluid is enriched with pro-inflammatory cytokines (e.g., TNF-α, IL-1β, IL-6) and activated immune cell subsets (e.g., Th1/Th17 cells and macrophages). These interact with FLS and synovial macrophages to induce aberrant proliferation of FLS and excessive secretion of matrix metalloproteinases (MMPs). The result is synovial hyperplasia, cartilage degradation, and bone erosion, culminating in the well-documented phenotype of erosive synovitis [7–9]. This highlights the liquid–solid interface as a crucial microenvironment where immune–stromal interactions amplify chronic inflammation.

In SLE, the deposition of circulating immune complexes on vascular endothelial surfaces provides another illustration of pathological interface responses. Complement activation (C1q, C3, C5b-9) induces endothelial injury and upregulates adhesion molecules such as VCAM-1 and ICAM-1, thereby promoting leukocyte infiltration and vasculitic changes. These processes underlie the multi-organ involvement characteristic of SLE, including glomerulonephritis, cutaneous lesions, and central nervous system inflammation [10,11].

Beyond joint and vascular pathology, mucosa-associated diseases such as inflammatory bowel disease (IBD) further exemplify the relevance of interface immunology. Studies have shown that gut microbiota and their metabolites can disrupt epithelial barrier integrity through immune responses at the intestinal–epithelial interface, thereby contributing to systemic immune dysregulation [12,13]. Such findings suggest the existence of a broader gut–immune–joint axis, wherein mucosal immune abnormalities may influence systemic autoimmune pathogenesis. This perspective not only deepens our understanding of autoimmune disease mechanisms but also identifies potential therapeutic entry points targeting interface-specific pathways.

2.3 Implications for Integrative Research

Taken together, these observations highlight the liquid–solid interface as a converging platform for inflammatory signaling, cellular cross-talk, and chronic tissue injury across different autoimmune diseases. While substantial progress has been made in delineating its molecular mediators, a comprehensive framework linking these immunological mechanisms with broader systemic interactions—such as the gut–immune–joint axis—remains underdeveloped. In this context, comparative perspectives, including those from traditional Chinese medicine theories (e.g., “phlegm–blood stasis interaction”), may offer valuable conceptual tools to enrich mechanistic interpretation. This underscores the need for integrative review and cross-disciplinary dialogue to better define the pathogenic and therapeutic significance of interface immune responses in autoimmune diseases.

3. Theoretical Evolution and Clinical Characteristics of the TCM Pathogenesis of “Phlegm–Blood Stasis Interaction”

Traditional Chinese medicine (TCM) has long regarded “phlegm-dampness obstructing the collaterals” as a key pathogenic mechanism underlying chronic and refractory disorders, including autoimmune conditions such as bi (painful obstruction syndrome) and wei (flaccidity syndrome). With the advancement of clinical and theoretical understanding, it has been observed that persistent phlegm-dampness often combines with blood stasis, giving rise to the more complex pathogenesis of “phlegm–blood stasis interaction”. This pathological process results in obstruction of the collaterals and internal accumulation of inflammatory heat, which frequently marks a critical turning point in the progression of disease, leading to chronicity, intractability, and recurrent flares [14]. Importantly, this concept not only reflects the distinctive TCM interpretation of persistent inflammation and interface pathology, but also provides a theoretical foundation for comparative studies between TCM and modern immunology.

3.1 Mechanisms of Phlegm-Dampness Formation and Evolution

Phlegm is recognized in TCM as one of the major pathological products. It typically arises from dysfunction of the spleen in transporting and transforming fluids, leading to the accumulation of dampness. Exogenous pathogenic dampness, dietary irregularities, and emotional disturbances

may also contribute to its generation. Phlegm is characterized by heaviness, turbidity, and stickiness, which predispose it to linger within joints and meridians, causing symptoms such as heaviness, distension, and numbness.

If unresolved, stagnant phlegm-dampness may transform into heat, and in combination with qi stagnation and blood stasis, progressively evolve into the condition of "phlegm–blood stasis interaction." This represents a deepening of the phlegm-dampness pathogenesis [15,16]. Once formed, phlegm–blood stasis complexes are adhesive and difficult to disperse, often lodging in synovial membranes and collateral vessels—the "interface" sites—where they recurrently trigger abnormal immune responses. Consequently, chronic inflammation persists, and the disease course becomes more complicated and variable.

3.2 Pathogenic Mechanisms and Clinical Manifestations of "Phlegm–Blood Stasis Interaction"

The interaction of phlegm-dampness with blood stasis readily leads to collateral obstruction and impaired circulation of qi and blood. Clinically, mild cases present with limb heaviness and limited mobility, while severe cases manifest as joint redness, swelling, pain, deformity, or even involvement of the sensory or cognitive orifices, producing symptoms such as head distension, cognitive sluggishness, fatigue, and lassitude. These "gel-like obstructive" manifestations reflect the coexistence of chronic inflammation and immune activation at interface sites [17].

From the perspective of modern pathology, this aligns closely with the processes occurring at the liquid–solid interface, including adhesion and activation of inflammatory mediators and perpetuation of immune responses. Particularly in RA, SLE, and ankylosing spondylitis (AS), the clinical signs associated with "phlegm–blood stasis interaction"—such as redness, swelling, stiffness, and recurrent attacks—provide a compelling explanatory model for the evolution of pathogenesis and symptomatology in autoimmune diseases.

3.3 Syndrome Differentiation and Clinical Features of "Phlegm–Blood Stasis Interaction"

"Phlegm–blood stasis interaction" represents a pivotal pathological mechanism across a wide spectrum of autoimmune diseases, notable for its complexity, evolving nature, and diagnostic challenges. In clinical practice, this pattern manifests in diverse forms depending on disease duration, the degree of heat involvement, and the extent of joint impairment. At the early stage, patients often present with phlegm-damp obstruction, characterized by limb heaviness, joint stiffness, general fatigue, a white greasy tongue coating, and a soft, slow pulse. As the disease progresses, damp-heat accumulation may emerge, reflected in clinical signs such as joint redness, swelling, burning pain, sticky sensation in the mouth without thirst, red tongue with yellow greasy coating, and a slippery rapid pulse. With chronicity and unresolved pathology, the syndrome frequently evolves into the phlegm–blood stasis interaction type, marked by joint deformity, pronounced functional impairment, dark tongue or stasis spots, and a choppy pulse, indicative of collateral obstruction by both phlegm and blood stasis. In some patients, phlegm misting the orifices becomes apparent, presenting as head distension, dizziness, cognitive dullness, and difficulty concentrating, often accompanied by fatigue, poor appetite, and epigastric oppression—symptoms that closely resemble the modern clinical description of "brain fog" [18].

These patterns are not fixed entities but may transform into one another or coexist in overlapping forms, requiring clinicians to adopt a dynamic and integrative approach to syndrome differentiation. Such classification provides a crucial basis for individualized TCM therapeutic strategies, while also offering a conceptual framework for understanding how "interface pathology" manifests at different stages of disease progression. Taken together, the syndrome patterns of "phlegm–blood stasis interaction" reveal a dynamic continuum from initial phlegm-damp accumulation to damp-heat obstruction and, ultimately, to persistent adhesive complexes embodying both phlegm and stasis. This clinical trajectory resonates strongly with the progressive immunopathology observed at liquid–solid interfaces, where inflammatory mediators, adhesion molecules, and tissue remodeling processes sustain chronic inflammation. By emphasizing parallels between evolving TCM syndromes and interface-driven immune responses, this perspective not only enhances the explanatory capacity of TCM theory in autoimmune diseases but also lays the groundwork for cross-disciplinary dialogue on the shared mechanisms of chronic inflammation and tissue damage.

4. Comparative Analysis of the Mechanisms of "Liquid–Solid Interface Immune Response" and the TCM Concept of "Phlegm–Blood Stasis Interaction"

The liquid–solid interface immune response has emerged in recent years as a major focus in immunological research. Its defining features include the adhesion, activation, and cascade amplification of inflammatory mediators at "liquid–solid boundary" sites such as the synovium, vascular endothelium, and mucosal surfaces. These processes ultimately result in local tissue injury and may further propagate systemic inflammation. By contrast, the traditional Chinese medicine (TCM) pathogenesis of phlegm–blood stasis interaction emphasizes the adhesive and lingering nature of pathological products, which persist over time, generate heat, obstruct the meridians, and gradually evolve into chronic bi syndromes. Although originating from fundamentally different medical paradigms, the two frameworks demonstrate striking parallels in several key dimensions, including sites of onset, pathogenic mediators, mechanisms of progression, and clinical manifestations. Both describe pathological processes driven by stagnation, adhesion, and persistent activation at boundary regions, culminating in chronic inflammation and tissue damage. To more intuitively illustrate the correspondences between these perspectives, the critical mechanisms of each are presented in a comparative format (Table 1).

Table 1: Comparative Analysis of the Mechanisms of "Liquid–Solid Interface Immune Response" and the TCM Concept of "Phlegm–Blood Stasis Interaction"

Dimension	Liquid–Solid Interface Immune Response	TCM Concept of "Phlegm–Blood Stasis Interaction"
Sites of onset	Synovial fluid–synovial membrane interface, vascular endothelium, intestinal–epithelial interface	Meridians, collaterals, joint cavities, interstitial spaces of zang-fu organs
Pathogenic mediators	Pro-inflammatory cytokines such as TNF-α, IL-6, IL-1β; complement components; adhesion molecules	Phlegm-dampness (heavy, turbid, adhesive), blood stasis (stagnant circulation), damp-heat pathogens
Pathological features	High concentrations of mediators adhere, activate, and amplify inflammation, sustaining chronic pathology	Phlegm and stasis congeal and persist, obstructing collaterals, with progressive emergence of heat signs
Evolutionary process	Cytokine aggregation → cellular adhesion and activation → persistent inflammation → tissue destruction	Dampness enduring → transformation into phlegm → phlegm–stasis congealing → accumulation of heat → refractory obstruction
Clinical manifestations	Joint swelling and pain, morning stiffness, fatigue, cognitive decline, brain fog, chronic fatigue	Redness, swelling, heat, and pain; heaviness and numbness; limited joint mobility; dizziness, fatigue, intractable bi syndrome
Mechanistic characteristics	Abnormal micro-interface inflammation, where local immune activation drives systemic effects	Phlegm and stasis obstruct collaterals, local stagnation leading to systemic qi and blood disharmony
Intervention strategies	Blockade of pro-inflammatory mediators, inhibition of cell adhesion, regulation of signaling pathways (e.g., NF-κB, MAPK)	Clearing heat and resolving phlegm, dispelling dampness and activating blood circulation, unblocking collaterals and relieving obstruction, harmonizing qi and blood
Advantages of TCM	Multi-target regulation of inflammatory interfaces; systemic, multi-mechanistic intervention	Flexible formula composition, precise syndrome differentiation, integration of holistic regulation with localized treatment

As shown in the table above, the liquid–solid interface, as the "activation platform" for modern immune-inflammatory responses, demonstrates a high degree of mechanistic analogy with the TCM concept of "phlegm–blood stasis interaction" and its pathological progression to "gel-like obstruction" in bi syndrome. Both mechanisms share common features, such as the concentration of pathology at tissue interfaces, the persistence of adhesive mediators that are difficult to clear, and the chronic evolution of inflammation that resists resolution. This analogy is particularly relevant in autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus, where the coexistence of local synovitis and systemic immune dysregulation further highlights the clinical value of these comparative pathophysiological models.

5. Research Progress on Traditional Chinese Medicine Interventions in "Liquid–Solid Interface Immune Response"

In recent years, as the understanding of local inflammatory mechanisms in autoimmune diseases has deepened, the "liquid–solid interface immune response" has gained widespread attention as a key link in the persistence of inflammation and tissue damage. This response commonly occurs at interface structures such as the synovial fluid–synovial membrane, plasma–endothelium, and intestinal–epithelial boundaries. It involves processes like the accumulation of inflammatory mediators, immune cell adhesion, and signal activation, driving inflammation from local sites to systemic involvement. These processes closely align with the TCM pathogenesis of "phlegm–blood stasis interaction, obstruction of the collaterals, and long-standing bi syndrome."

Due to its holistic regulatory nature and multi-target intervention, Traditional Chinese Medicine (TCM) has demonstrated unique advantages in alleviating interface-related inflammatory abnormalities. Commonly used formulas, such as Si Miao Wan, Er Miao Wan, and Long Dan Xie Gan Tang, are effective in treating conditions such as damp-heat obstruction, heaviness in the lower limbs, and joint redness and swelling. Modern research suggests that these formulas may intervene in inflammatory pathways like TNF-α and IL-1β, modulate synovial cell adhesion states, and relieve local interface inflammation [19-21]. Formulas like Chai Hu Shu Gan San and Da Huang Mu Dan Tang are used to regulate liver function, resolve stagnation, and clear heat, making them particularly suitable for treating SLE patients with a "phlegm-heat disturbing the upper" pattern. These formulas have been shown to improve central nervous system symptoms like brain fog and fatigue, as well as regulate the neuro-immune interface environment [22,23].

Additionally, formulas such as Huang Lian Jie Du Tang and Yin Chen Hao Tang are widely used for patients with "heat-toxins obstructing" or "damp-heat and blood stasis" conditions. Studies indicate that these formulations can affect signaling axes such as TLR/NF-κB and NLRP3, thereby alleviating inflammatory responses between vascular and endothelial tissues [24,25]. Beyond traditional formulations, individual TCM compounds such as quercetin, tanshinone II A, and baicalin have also made progress in the field of interface anti-inflammation. These compounds can influence cell adhesion, chemotaxis, and inflammatory mediator expression. Some studies are exploring their application in modern pharmaceutical forms, such as nano-delivery systems and targeted carriers, to enhance their accumulation and bioavailability in local microenvironments, offering new directions for precise TCM interventions in liquid–solid interface inflammation [26-28].

6. Conclusion and Prospects

The pathogenesis of Traditional Chinese Medicine (TCM) "phlegm and blood stasis" and the modern medical concept of "liquid-solid interface immune response" exhibit a high degree of correspondence in autoimmune diseases. The former provides a macro interpretation of the pathological state at the interface, while the latter reveals the cellular and molecular mechanisms underlying the persistence of inflammation. Chinese herbal formulas and their active components intervene in the interface inflammation process through multiple targets and pathways, demonstrating significant therapeutic potential. Future research can further establish more representative interface pathological models, such as synovial cell-immune cell co-culture systems and endothelial-monocyte adhesion models, to simulate the "liquid-solid interface" inflammatory environment and

provide experimental support for the mechanisms of Chinese medicine intervention. At the same time, efforts should be made to strengthen the integration of TCM syndrome differentiation and the omics of the interface microenvironment. By utilizing techniques such as single-cell sequencing, spatial transcriptomics, and proteomics, the intrinsic connection between syndrome classification and local inflammation can be explored, achieving precise matching between "syndrome-interface-target." Furthermore, the fusion of clinical and basic research should be promoted to verify the efficacy, integrating clinical symptoms, experimental indicators, and changes in inflammatory signaling pathways, thus establishing a three-dimensional translational research framework of "symptoms-pathology-mechanisms" to enhance the scientific and explanatory basis of TCM interventions. In conclusion, using "phlegm and blood stasis" to map the "liquid-solid interface response" serves as an entry point to modernize the expression of TCM pathogenesis, expand the theoretical depth and practical breadth of Chinese medicine in the systemic intervention of autoimmune diseases, and provide theoretical support and a research foundation for new diagnostic and therapeutic models under the framework of integrative medicine.

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