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The Central Role of Immunity and Inflammation in the Pathogenesis of Connective Tissue Disease-Associated Pulmonary Arterial Hypertension (CTD-PAH) and Therapeutic Targets

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Abstract: ***Connective tissue disease-associated pulmonary arterial hypertension (CTD-PAH) is a critical and often fatal complication in patients with conditions such as systemic sclerosis and systemic lupus erythematosus. Its pathological mechanism is complex, extending far beyond simple pulmonary vasoconstriction. Recent research confirms that the inherent immune dysregulation of CTDs and the consequent chronic inflammatory response are the core engines initiating and accelerating pulmonary vascular remodeling. This review systematically explains how autoantibodies, abnormally activated immune cells (T/B lymphocytes, macrophages, mast cells), and the subsequently released cytokine and chemokine network (e.g., IL-6, IL-1β, TNF-α, MCP-1) act in concert to cause endothelial injury, smooth muscle cell proliferation, and perivascular fibrosis, ultimately leading to irreversible vascular occlusion. Based on this mechanism, the article focuses on reviewing current therapeutic strategies targeting immune inflammation, including the evolution from conventional immunosuppressants to novel biological agents (such as rituximab, tocilizumab, JAK inhibitors), and the comprehensive management concept of "immunomodulation combined with vascular-targeted therapy."***

Keywords: Connective Tissue Diseases, Pulmonary Arterial Hypertension, Immunopathogenesis, Inflammation.

1. Introduction

Pulmonary arterial hypertension associated with connective tissue disease (CTD-PAH) is one of the most severe complications of conditions such as systemic sclerosis and systemic lupus erythematosus, and a key cause of mortality in these patients [1]. Compared with idiopathic pulmonary arterial hypertension, CTD-PAH carries a worse prognosis, suggesting the presence of distinct underlying pathogenic mechanisms. Traditionally, pulmonary arterial hypertension has been viewed primarily as a disorder of abnormal vasoconstriction in the pulmonary vasculature, and treatment has long focused on vasodilation. However, growing evidence in recent years indicates that CTD-PAH is, at its core, a vascular pathology driven by immune-mediated inflammation. The central concept is that the persistent autoimmune dysfunction and chronic inflammatory state inherent in CTD patients directly attack and remodel the structure of the pulmonary blood vessels. In lung tissue from patients with CTD-PAH, significant infiltration of immune cells — including T cells, B cells, macrophages, and others—can be observed around the small pulmonary arteries, forming an "inflammatory cuff." Simultaneously, levels of various inflammatory cytokines and chemokines are markedly elevated, creating a complex inflammatory microenvironment. Research has confirmed that the intensity of this inflammatory response closely correlates with disease severity and patient prognosis [2].

Thus, the current understanding of CTD-PAH has undergone a fundamental shift: it is no longer seen merely as a hemodynamic disorder, but rather as a disease characterized by progressive pulmonary vascular remodeling, driven by aberrant activation of the immune system. Understanding the central role of immunity and inflammation in its pathogenesis not only reveals the essential nature of the disease but also provides a solid theoretical foundation for developing new strategies that go beyond traditional vasodilatory therapies — namely, therapies that target the inflammatory and immune [3].

2. The Immuno-Inflammatory Network Drives the Cascade of Pulmonary Vascular Remodeling

The conventional view that pulmonary arterial hypertension arises primarily from an imbalance between vasoconstriction and vasodilation has been fundamentally redefined in the context of CTD-PAH. Its essence is now understood as a local manifestation of CTD-related autoimmune dysregulation at the level of the pulmonary vasculature. Aberrant immune activation and the ensuing chronic inflammatory response together constitute the central pathway driving the progressive

and irreversible remodeling of pulmonary blood vessels [4].

2.1 The Initiating Role of the Autoimmune Response

The origin of CTD-PAH can be traced to the specific autoantibodies produced by patients. These antibodies are not mere bystanders but function as direct "molecular weapons" attacking the pulmonary vasculature. For instance, in patients with systemic sclerosis (SSc), antibodies such as anti-U3-RNP and anti-endothelial cell antibodies (AECAs) can specifically bind to antigens on the surface of pulmonary vascular endothelial cells. This binding inflicts direct endothelial damage through at least two key mechanisms: First, by activating the complement system, leading to the formation of membrane attack complexes or the generation of potent chemoattractants like C5a, which trigger inflammation. Second, through antibody-dependent cellular cytotoxicity (ADCC), recruiting immune cells such as natural killer cells to lyse endothelial cells [5]. The compromise of this critical barrier between blood and tissue not only increases vascular permeability but also initiates a shift in endothelial cells from a quiescent state to an activated, apoptotic, or aberrantly proliferative phenotype. This event serves as the opening act, setting the stage for the subsequent complex processes of inflammation and remodeling [4].

2.2 Immune Cell Infiltration and Functional Dysregulation

Injured endothelial cells release chemotactic signals, acting as an "alarm beacon" that recruits various immune cells to the perivascular area, forming the so-called "inflammatory cuff." This infiltrating cellular collective is not a disorganized crowd but a dysfunctional, interactive ecosystem. T Lymphocytes: Among these, the imbalance in $CD4^+$ T helper cell subsets is particularly critical. T helper 17 (Th17) cells are of major importance, as their signature effector cytokine, interleukin-17 (IL-17), is a powerful pro-inflammatory mediator. IL-17 can stimulate vascular endothelial cells, fibroblasts, and others to produce more IL-6 and chemokines (e.g., CXCL8), further amplifying the inflammatory response and recruiting neutrophils. In contrast, regulatory T cells (Tregs), which normally counteract excessive inflammation, are often found to be reduced in number or functionally impaired in CTD-PAH patients [2].

This failure of the immune "brake" allows inflammation to proceed unchecked. Additionally, cytotoxic T lymphocytes (CTLs) may directly participate in the killing of endothelial cells.B Lymphocytes: The role of B cells in CTD-PAH is multifaceted. They serve not only as the "factories" producing pathogenic autoantibodies but also as potent antigen-presenting cells that can activate T-cell responses. Furthermore, activated B cells themselves secrete pro-inflammatory cytokines like IL-6, thereby forming a positive feedback loop with T cells and other players that perpetuates and intensifies local inflammation. Studies have even identified clonally expanded B-cell populations within the pulmonary vascular lesions of patients, suggesting the possibility of antigen-driven B-cell activation at the disease site. Macrophages/Monocytes: Guided by chemokines such as Monocyte Chemoattractant Protein-1 (MCP-1/CCL2), monocytes are recruited to the vascular wall and differentiate into macrophages [6].

Within the inflammatory milieu of CTD-PAH, these macrophages often polarize towards a pro-inflammatory M1 phenotype. Acting as both "amplifiers" and "effectors" of inflammation, they release large quantities of key mediators including tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), platelet-derived growth factor (PDGF), and transforming growth factor-beta (TGF-β). These substances directly drive the proliferation and migration of vascular smooth muscle cells and promote fibrosis in the vascular adventitia. Mast Cells and Dendritic Cells: The number of mast cells is significantly increased around affected pulmonary vessels. Upon degranulation, they release mediators such as tryptase, chymase, histamine, and leukotrienes, which can directly promote vasoconstriction, smooth muscle cell proliferation, and collagen deposition, playing a role in the early stages of vascular structural remodeling. The infiltration of dendritic cells is closely associated with the capture, processing, and presentation of local antigens, thereby initiating and sustaining the adaptive immune response [7].

2.3 The Cytokine and Chemokine Storm: The Core Signaling Network

The functions of the aforementioned immune cells are largely executed through the diverse array of inflammatory mediators they secrete. These mediators intertwine to form a complex signaling network that dictates the disease progression.

Core Pro-inflammatory Cytokines: Interleukin-6 (IL-6) is regarded as a critical hub within this network. It activates multiple signaling pathways, including JAK/STAT and MAPK, within endothelial and smooth muscle cells via both classical and trans-signaling pathways. This activation promotes cell proliferation, inhibits apoptosis, and can positively regulate the differentiation of Th17 cells. Clinical research confirms that serum IL-6 levels in patients significantly correlate with disease activity and poor prognosis in CTD-PAH.IL-1β and TNF-α are potent initiators and drivers of the inflammatory response [8].

They activate key transcription factors such as nuclear factor-kappa B (NF-κB), upregulating the expression of adhesion molecules on vascular endothelial cells. This promotes increased adhesion and infiltration of leukocytes and causes direct or indirect tissue damage. Animal models of experimental pulmonary hypertension have demonstrated that inhibiting IL-1βor TNF-α can effectively attenuate vascular remodeling. Core Pro-fibrotic Factor: Transforming Growth Factor-Beta (TGF-β) acts as the central "molecular bridge" linking inflammation to fibrosis. Produced by activated macrophages, endothelial cells, and others, it powerfully stimulates the trans differentiation of fibroblasts surrounding the pulmonary vessels into myofibroblasts. Myofibroblasts possess a robust secretory capacity, leading to excessive deposition of extracellular matrix components, particularly collagen [9].

This process is a core mechanism responsible for vascular wall thickening, stiffening, and luminal narrowing. The Chemokine Network: Molecules such as CX3CL1

(Fractalkine), MCP-1 (CCL2), RANTES (CCL5), and SDF-1α (CXCL12) function as precise "chemical navigation" systems. They specifically guide monocytes, lymphocytes, dendritic cells, and others to migrate towards the site of vascular pathology, forming the cornerstone for establishing and maintaining the local inflammatory microenvironment [1].

2.4 The Common Final Pathway of Downstream Vascular Remodeling

The sustained onslaught of immune attacks and inflammatory signaling ultimately converges into three core pathological hallmarks of "malignant" pulmonary vascular restructuring: Endothelial Dysfunction: Characterized by reduced synthesis of vasodilatory and anti-proliferative agents like nitric oxide and prostacyclin, coupled with increased production of the potent vasoconstrictor and pro-proliferative agent endothelin-1 (ET-1), disrupting vascular homeostasis. Abnormal Smooth Muscle Cell Proliferation and Migration: Stimulated by various growth factors and inflammatory cytokines, the medial smooth muscle cells undergo excessive proliferation and migrate from the media into the intima, leading to intimal thickening [10].

Adventitial and Perivascular Fibrosis: Activated adventitial fibroblasts proliferate and secrete vast amounts of extracellular matrix, resulting in overall vascular wall fibrosis and stiffening. Acting in concert, these changes lead to the formation of characteristic plexiform lesions and vascular occlusion. This causes a progressive and irreversible increase in pulmonary vascular resistance, imposing a continuously elevated afterload on the right ventricle and ultimately culminating in right heart failure [11].

3. Therapeutic Strategies Targeting Immune - Inflammation

The profound understanding of the central role played by immune-inflammation in the pathogenesis of CTD-PAH is driving a fundamental transformation in the therapeutic paradigm for this condition.

3.1 Foundational Immunosuppressive Therapy

Active and appropriate management of the activity of the underlying connective tissue disease is the prerequisite and foundation for all therapeutic decisions in CTD-PAH. Glucocorticoids, as potent non-specific anti-inflammatory and immunosuppressive agents, are often used during disease flare-ups to rapidly control systemic inflammation. However, their long-term use as monotherapy for pulmonary vascular disease has unclear benefits and significant side effects. Therefore, combination therapy with other immunosuppressants is more common [11].

Application in Specific CTD Types: For PAH associated with systemic lupus erythematosus (SLE), inflammatory myositis (PM/DM), or mixed connective tissue disease (MCTD), especially when patients present with clear evidence of systemic inflammatory activity (e.g., fever, arthritis, serositis, active myositis), aggressive immunosuppressive therapy can often yield significant benefits [10]. The combination of cyclophosphamide (oral or intravenous pulse) with glucocorticoids has been shown in multiple observational studies to improve pulmonary arterial pressure, functional class, and even partially reverse pulmonary vascular lesions in such patients. Mycophenolate mofetil, a relatively more selective immunosuppressant, is also accumulating evidence of efficacy, particularly showing potential in SLE-associated PAH. Its mechanism lies in broadly inhibiting lymphocyte proliferation and antibody production, thereby mitigating the immune system's attack on the vasculature.

3.2 Targeted Biologics and Novel Immunomodulators

Anti-CD20 Monoclonal Antibody (Rituximab): This drug achieves multi-layered immune intervention by specifically depleting CD20-expressing B lymphocytes: 1) Directly reducing the production of pathogenic autoantibodies; 2) Attenuating the ability of B cells to act as antigen-presenting cells and activate T cells; 3) Decreasing the secretion of B-cell-derived pro-inflammatory factors (e.g., IL-6), thereby breaking the positive feedback loop of immune inflammation. Numerous retrospective studies and case series reports indicate that rituximab can improve clinical symptoms (e.g., dyspnea), increase exercise capacity (6-minute walk distance), and, to some extent, stabilize or improve hemodynamic parameters (e.g., mean pulmonary arterial pressure, pulmonary vascular resistance) in patients with refractory SSc-PAH, particularly those with active skin involvement or poor response to conventional therapies. Recent high-quality retrospective cohort studies and open-label trials further support its potential efficacy and acceptable safety profile, making it one of the most widely used targeted biologic agents in current clinical practice [12].

Anti-IL-6 Receptor Monoclonal Antibody: Given the central hub position of IL-6 in the pathogenic network of CTD-PAH, blocking its signaling pathway has a strong theoretical rationale. Tocilizumab is a humanized monoclonal antibody that effectively blocks both classic and trans-signaling of IL-6 by competitively binding to soluble and membrane-bound IL-6 receptors [13]. In the overall treatment of SSc, multiple large randomized controlled trials have confirmed that tocilizumab significantly slows the progression of skin fibrosis and improves systemic inflammatory markers. These effects naturally sparked interest in its potential for treating SSc-PAH. Although results from a dedicated large Phase III randomized controlled trial for SSc-PAH are still awaited, preliminary studies and subgroup analyses have shown encouraging trends. Tocilizumab is believed to exert its potential therapeutic effects by inhibiting vascular inflammation, smooth muscle proliferation, and fibrosis, among other processes [14].

JAK Inhibitors: This class of oral small-molecule targeted drugs blocks the JAK-STAT signaling pathway downstream of multiple key cytokines, including IL-6, interferon-gamma, and IL-12/23, by inhibiting the activity of the tyrosine kinase JAK family. This pathway is a common node for the transduction of numerous pro-inflammatory and pro-fibrotic signals. JAK inhibitors (e.g., tofacitinib, baricitinib) have demonstrated excellent efficacy in CTDs such as rheumatoid arthritis and axial spondyloarthritis. Based on this, scientists are actively exploring their potential value in SSc and other

CTD-PAHs. Preliminary preclinical studies and case reports suggest promise, and some exploratory clinical trials are underway. JAK inhibitors offer a new, convenient oral option for targeted immunomodulatory therapy in CTD-PAH [15].

Other Potential Targets: The complexity of the immune-inflammatory network implies more potential points of intervention. For example, IL-1β inhibitors (e.g., anakinra) have shown signals of improved cardiopulmonary function in small clinical studies of idiopathic PAH, and their value in CTD-PAH warrants exploration. Complement system inhibitors (e.g., drugs targeting C5a) could theoretically block the vasculitic damage triggered by autoantibody-immune complex-mediated complement activation, and are currently at an earlier stage of investigation. The exploration of these targets reflects the trend toward more refined and diversified treatment strategies.

3.3 Combination Therapy Strategy

Immediate Initiation of Standard PAH-Targeted Therapy: Upon diagnosis of CTD-PAH, regardless of the activity level of the underlying disease, guideline-directed targeted drug therapy for pulmonary arterial hypertension itself should be initiated and optimized without delay. This includes, based on risk stratification, selecting monotherapy or combination therapy with endothelin receptor antagonists [16], phosphodiesterase type 5 inhibitor, and/or prostanoids. The goal of this step is to rapidly reduce pulmonary vascular resistance, improve right heart function, alleviate symptoms, and buy time and stability for the patient.

Individualized Assessment and Combination with Immunomodulation: Concurrent with or following the initiation of vascular-targeted therapy, a collaborative assessment by rheumatology and pulmonary vascular/ cardiology specialists is essential. This assessment should comprehensively evaluate the type of CTD and the level of systemic and pulmonary vascular inflammatory activity [17]. Based on the findings, an individualized immunomodulation plan should be formulated: For CTD-PAH with obvious active inflammation, such as in SLE or MCTD, aggressive foundational immunosuppressive therapy is reasonable. For refractory or progressive SSc-PAH, especially with relevant clinical features, consideration can be given to adding rituximab or enrolling in clinical trials for biologics like tocilizumab. The timing, choice, and combination of therapies need to be dynamically adjusted, with close monitoring of efficacy.

4. Conclusion and Future Perspectives

The central driving role of immunity and inflammation in the pathogenesis of connective tissue disease-associated pulmonary arterial hypertension (CTD-PAH) is now firmly established. The inherent immune dysregulation in CTD patients, mediated through specific autoantibodies, aberrantly activated immune cells (such as T and B lymphocytes, macrophages), and the complex cytokine and chemokine networks they release, collectively creates an inflammatory microenvironment that propels progressive and irreversible pulmonary vascular remodeling. This understanding has prompted a fundamental shift in the therapeutic paradigm for CTD-PAH: moving from a primarily reactive approach reliant on vasodilators to manage hemodynamic derangements, towards an active, comprehensive strategy of "immunomodulation combined with vascular-targeted therapy." The evolution of current treatment strategies is manifested in two key aspects: first, the active exploration and application of novel biological agents (e.g., rituximab, tocilizumab) and small-molecule drugs targeting specific immune pathways, aiming to intervene at the source of the disease process.

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