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Intrapulmonary T Cells Drive Schistosoma-induced Pulmonary Hypertension

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Introduction

Pulmonary Hypertension (PH) is a severe complication of chronic schistosomiasis, a parasitic infection caused by Schistosoma species. While the pathogenesis of schistosomiasis-associated PH is complex, recent evidence highlights the crucial role of the immune system, particularly intrapulmonary T cells, in driving the development and progression of this condition. This report explores the mechanisms by which intrapulmonary T cells contribute to Sch-PAH, including inflammation, immune dysregulation, and vascular remodeling. Understanding these processes could open avenues for targeted immunotherapies aimed at preventing or mitigating PH in schistosomiasis patient. Schistosomiasis is a parasitic disease caused by Schistosoma species, affecting millions of individuals worldwide, particularly in tropical and subtropical regions. Chronic infection can lead to several complications, including portal hypertension, liver fibrosis, and in some cases, pulmonary hypertension. Schistosomiasis-induced pulmonary hypertension has become an important clinical entity, recognized for its significant morbidity and mortality.

Description

Sch-PAH develops when Schistosoma eggs lodge in the pulmonary vasculature, leading to chronic inflammation, vascular remodeling, and eventually increased Pulmonary Vascular Resistance (PVR). This increase in PVR results in elevated Pulmonary Arterial Pressure (PAP) and right heart strain, a hallmark of pulmonary hypertension. While prior research has focused on the role of granulomatous inflammation and fibrosis, emerging evidence underscores the role of intrapulmonary T cells in orchestrating the immune response that leads to PH. In this report, we discuss the role of intrapulmonary T cells in Sch-PAH, focusing on the mechanisms of immune-mediated pulmonary vascular remodeling, inflammation, and the potential for targeting these immune cells in future therapies. A 36-year-old male patient from a schistosomiasis-endemic region presented to the clinic with worsening exertional dyspnea, fatigue, and lower extremity edema over the past six months. He had a known history of chronic schistosomiasis, confirmed by positive serology for Schistosoma mansoni. The patient had previously received treatment with praziquantel but continued to have chronic symptoms [1].

Physical examination revealed an elevated jugular venous pressure, hepatomegaly, and lower limb edema, suggestive of right heart failure. Auscultation of the lungs was clear, but heart sounds revealed a loud P2 component. Further investigation through transthoracic echocardiography showed right ventricular hypertrophy and an elevated right ventricular systolic pressure (RVSP) of 75 mmHg, highly suggestive of pulmonary hypertension. Right heart catheterization confirmed the diagnosis of Pulmonary Arterial Hypertension (PAH) with a mean pulmonary arterial pressure of 42 mmHg and a pulmonary vascular resistance (PVR) of 5 Wood units. High-Resolution Computed Tomography (HRCT) of the chest revealed vascular congestion, while chest X-ray and pulmonary function tests were unremarkable aside from mild restrictive changes. Given the history of schistosomiasis, laboratory testing was conducted to rule out other potential causes of PAH, and Sch-PAH was confirmed. Inflammatory markers were elevated, particularly those linked to T cell activation, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha,leading to further investigation into the immune mechanisms contributing to the patient's condition [2].

In schistosomiasis, Schistosoma eggs are known to lodge in the pulmonary vasculature after traversing the liver, particularly in patients with chronic infection. The presence of these eggs triggers a robust immune response dominated by granuloma formation. Although granulomas are typically associated with macrophages, eosinophils, and other innate immune cells, T cells also play a crucial role in coordinating this response. T helper cells (especially Th1 and Th17 subsets) become activated in response to antigens from Schistosoma eggs. These activated T cells migrate to the lungs and secrete pro-inflammatory cytokines such as interferon-gamma (IFN-γ), IL-6, and IL-17, which amplify the local immune response. This cytokine milieu promotes further recruitment of immune cells, leading to persistent inflammation and tissue damage. A major feature of Sch-PAH is pulmonary vascular remodeling, characterized by smooth muscle cell proliferation, intimal thickening, and perivascular fibrosis [3].

Pro-inflammatory cytokines produced by T cells, particularly IFN-γ and IL-17, promote the activation of pulmonary endothelial cells and smooth muscle cells, driving their proliferation. IL-17, in particular, has been shown to enhance smooth muscle cell migration and vascular remodeling in experimental models of PH. Activated T cells stimulate fibroblasts, leading to collagen deposition and fibrosis around the pulmonary vasculature. This process exacerbates the narrowing of the pulmonary arteries, further increasing PVR. T cell-derived cytokines contribute to endothelial cell dysfunction by promoting the expression of adhesion molecules and inflammatory mediators. This leads to an altered endothelial phenotype, marked by reduced Nitric Oxide (NO) production and increased production of endothelin-1 both of which favor vasoconstriction and vascular remodeling. An imbalance between effector T cells (e.g., Th1 and Th17 cells) and regulatory T cells (Tregs) is thought to play a role in the pathogenesis of Sch-PAH. Normally, Tregs act to suppress excessive immune responses and prevent tissue damage [4].

However, in Sch-PAH, there is evidence of a relative deficiency in Treg function or number, which may allow unchecked inflammation and immune-mediated vascular damage. The loss of immune regulation may also contribute to the persistence of inflammation even after the initial infection has been treated, as seen in patients who develop PH years after exposure to Schistosoma. This immune dysregulation perpetuates the cycle of inflammation and vascular remodeling, eventually leading to chronic PH. Several studies using experimental models of schistosomiasis have provided valuable insights into the role of intrapulmonary T cells in Sch-PAH. Mice infected with Schistosoma mansoni develop pulmonary hypertension and vascular remodeling similar to that observed in humans. In these models, T cell depletion or inhibition of key cytokines (such as IL-17 or IFN-γ) has been

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shown to reduce pulmonary vascular remodeling and lower PAP, confirming the pathogenic role of T cells in this process.

Furthermore, animal models have demonstrated that adoptive transfer of T cells from infected mice to healthy mice induces pulmonary vascular changes, providing direct evidence of T cell involvement in the development of Sch-PAH. These findings suggest that targeting specific T cell subsets or their cytokines could be a viable therapeutic strategy for patients with Sch-PAH. Given the prominent role of T cells in the pathogenesis of Sch-PAH, targeting these immune cells may offer novel therapeutic options. Inhibiting key cytokines involved in T cell-mediated inflammation, such as IL-6, IL-17, or TNF-α, could reduce inflammation and vascular remodeling in Sch-PAH. Clinical trials in other forms of PH have shown promise with cytokine inhibitors, and these agents could be repurposed for Sch-PAH. Therapies aimed at restoring the balance between effector T cells and Tregs, such as low-dose interleukin-2 (IL-2) or immune checkpoint inhibitors, may help to regulate the immune response and prevent ongoing vascular damage. Medications that modulate the immune system, such as corticosteroids or immunosuppressants, could be considered in severe cases of Sch-PAH where inflammation is driving disease progression. Drugs targeting fibroblast activation and collagen deposition, such as pirfenidone or nintedanib, which are used in idiopathic pulmonary fibrosis, may also have a role in reducing vascular fibrosis in Sch-PAH [5].

Conclusion

Intrapulmonary T cells play a crucial role in the development and progression of schistosomiasis-associated pulmonary hypertension through their involvement in chronic inflammation, vascular remodeling, and immune dysregulation. The insights gained from this report highlight the importance of immune mechanisms in Sch-PAH and suggest potential therapeutic targets aimed at modulating T cell activity. As Sch-PAH continues to pose a significant health burden in endemic areas, understanding the immune-driven pathogenesis of the disease is essential for the development of novel treatments. Further research, including clinical trials targeting T cells and their associated cytokines, is necessary to determine the most effective strategies for managing this complex condition.

Acknowledgement

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Conflict of Interest

None.

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