Transforming Growth Factor-β Signaling in Schistosomiasis-Induced Pulmonary Hypertension
A Perspective for Antifibrotic Drugs?

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Schistosomiasis is a parasitic disease affecting a large portion of the global human population and represents one of the most common causes of pulmonary hypertension (PH) around the world.1-3 Schistosomiasis-associated pulmonary arterial hypertension (PAH) is classified in the group 1.4,5, according to the current clinical classification of pulmonary hypertension from Dana Point in 2008.4 It has been suggested that pulmonary vascular remodeling in response to Schistosoma infection is similar to other forms of PAH, such as idiopathic PAH.1 In addition, the presence of prominent granulomatous inflammation and fibrosis has been described.1.5.6 In recent years, we have noticed that augmented inflammation is indeed an unavoidable player in the pathology of idiopathic PAH, and the literature suggests that chronic inflammation is an important culprit in pathogenesis of schistosomiasis-associated PAH, as well.1.2.7 Despite the novel advances in the field, the exact underlying mechanisms and contribution of inflammation to the pathogenesis of this disease is still not fully resolved, and future studies remain necessary.

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Recognizing this need, Graham et al8 publish findings in this issue of Circulation that contribute significantly to the knowledge of the role of transforming growth factor (TGF)-β signaling pathway and Th2 inflammation in the complex pathology of experimental schistosomiasis-induced PH. Focusing on the involvement of TGF-β in this disease, the authors demonstrate that pharmacological inhibition of TGF-β signaling and the lack of Smad3 results in a protection against Schistosoma-induced PH. In addition, a significant increase of TGF-β1 mRNA was found in mice exposed to Schistosoma, and, importantly, the observed augmentation seems to depend on the Th2 cytokines interleukin (IL)-4 and IL-13. In this context, the literature underlined the contribution of IL-4 and IL-13 in the pathology of schistosomiasis-induced PH.9.10 The plasma levels of IL-4 and IL-13 have increased over time in infected mice, and experimental schistosomiasis-induced PH is potentially dependent on exaggerated IL-13 signaling.9.10 Extending this knowledge, Graham and colleagues show the significant reduction in IL-4 and IL-13 concentrations on the blockade of TGF-β signaling, implying the existence of a positive feedback loop of TGF-β1 and Th2 cytokines IL-4/IL-13.8 Finally, to prove the relevance of the experimental concept and findings, the authors successfully demonstrate the evidence of TGF-β signaling in the remodeled pulmonary vessels of the patients with schistosomiasis-associated PAH.8 Considered as a whole, the data from Graham and coworkers not only provide valuable scientific information, but also indicate that the therapeutic breakage of circulus vitiosus created between TGF-β1 and IL4/IL13 may represent a more specific strategy for the future treatment of this PAH form in comparison with antiparasitic drugs such as praziquantel.8.11 Interestingly, altered TGF-β signaling is recognized as a crucial pathological player in development of idiopathic pulmonary fibrosis. Targeting this pathway with pirfenidone represents the current approved therapeutic option for idiopathic pulmonary fibrosis.12.13 In this context, one can expect that drugs such as pirfenidone may be used to interrupt the existing pathological circle of TGF-β and IL4/IL13 by inhibiting the TGF-β. Additionally, this antifibrotic drug has been shown to successfully reduce IL-4 and IL-13 levels in a model of airway remodeling and inflammation, suggesting the potential efficacy of pirfenidone in targeting not only the TGF-β, but also all members of the evil trio.14 In light of these findings, we recommend that future studies focus on elucidating whether the therapeutic application of pirfenidone, as a promising inhibitor of the TGF-β-IL-4-IL-13 cycle, will provide beneficial effects in the context of schistosomiasis-associated PAH.

Disclosures

None.

References


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