Thrombospondin-1 in pulmonary arterial hypertension: what ails NOS?

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This editorial refers to ‘Activated CD47 promotes pulmonary arterial hypertension through targeting caveolin-1’ by P.M. Bauer et al., pp. 682–693, this issue.

Pulmonary arterial hypertension (PAH) is a debilitating progressive disease with a poor prognosis. The median survival for idiopathic pulmonary hypertension was 2.8 years; advances in specifically targeted therapeutics have improved the prognosis significantly, but mortality remains high. Irrespective of the cause of PAH, there is evidence of severe vascular endothelial dysfunction within the pulmonary circulation with characteristic findings of vascular medial hypertrophy and intimal fibrosis, occasionally with luminal narrowing. This leads to increased pulmonary vascular resistance, persistent vasoconstriction, and eventually right ventricular hypertrophy and dysfunction.

The crux of the conceptual problem limiting the current understanding of the pathophysiology of PAH is whether there is a specific single primary cause underlying the pharmacologically diffuse phenomenon of pulmonary endothelial dysfunction. Indeed, the current therapeutic approaches to the management of pulmonary hypertension represent a ‘blunderbuss approach’ to pulmonary vascular reactivity, with both a number of targeted pathways (endothelin, nitric oxide (NO), prostacyclin) modulated as well as the non-specific approach of treatment with L-type calcium antagonists. Even in circumstances where a single mutation underlies the development of PAH, there has been no corresponding ‘targeting’ of therapy.

While there are multiple potential synergistic interactions between potentiation of NO and prostacyclin signalling and inhibition of the endothelin effect, the only successful therapeutic approach primarily targeting the NO–solute guanylate cyclase (sGC) pathway to date has involved agents such as sildenafil which potentiate the effects of cGMP and, hence, of released NO.

The past few years have seen three relatively unrelated pieces of potential progress targeting the NO–sGC pathway. First, pulmonary hypertension has been experimentally linked in a number of models with impairment of sGC activity. Experimental data support the utility of both direct stimulators of sGC (e.g. BAY 58-2667 (cinaciguat)), although it is uncertain to what extent sGC dysfunction in PAH results from haem depletion of sGC.

Secondly, a study from the Gladwin laboratory in 2010 raised the possibility that nitrite (NO\(_2^-\)) might be uniquely effective in both preventing and reversing PAH. Nitrite bioactivation by hypoxia provides it with a unique mechanism for interaction with PAH, and indeed, the preliminary data in animal models were exciting. However, NO released from NO\(_2^-\) acts preferentially on ‘healthy’ sGC, and it is therefore theoretically possible that its efficacy might be diminished in PAH and/or that it might induce excessive systemic vasodilatation and hypotension. Clinical studies with nitrate are of paramount interest.

A study by Bauer et al. is notable for the presentation of a new development that is potentially critical to the understanding of the pathophysiology of the NO–sGC system in PAH. This study highlights the potential role of thrombospondin-1 (TSP-1) and its principle receptor CD47 in the pathogenesis of PAH. In a series of elegant studies, these investigators provided substantial evidence that TSP-1 synthesis is stimulated in PAH, with approximately three-fold increases in expression of TSP-1 in lungs of patients with both primary and secondary PAH. Similarly, in mice exposed to acute hypoxia, there was rapid induction of pulmonary TSP-1 expression. Furthermore, TSP-1 was able to activate its principal receptor CD47 to alter the constitutive interaction between CD47 and caveolin, leading to ‘uncoupling’ of endothelial NO synthase (eNOS) and the generation of reactive oxygen species. In association with these molecular changes, there was proliferation of muscularized pulmonary arterioles, leading to the development of right ventricular hypertrophy.

Several aspects of these findings are exciting. TSP-1 is a matricellular protein that has been previously shown to act, in similar picomolar concentrations, as an sGC inhibitor, thereby impairing NO-stimulated cGMP production and NO signalling. The possibility that NOS represents an additional ‘target’ for TSP-1/CD47 activation provides it with a unique mechanism for interaction with PAH, and of direct activators selective for haem-depleted sGC [e.g. BAY 58-2667 (cinaciguat)], although it is uncertain to what extent sGC dysfunction in PAH results from haem depletion of sGC.

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rationale for the use of direct sGC activation, as well as NO$_3^-$, which act via NOS-independent pathways. An integrated view of the pathogenetic and therapeutic implications of these findings is shown in Figure 1.

The principal caveat of the current study is that while it clearly implicates TSP-1 as a component of the pathogenesis of PAH, it does not differentiate between a primary and a secondary/potentiating role for TSP-1/CD47 signalling. On the one hand, Maloney et al. have recently demonstrated that TSP-1 gene mutations may coexist with those in bone morphogenetic protein receptor 2 gene (BMPR2) in familial PAH, perhaps accounting for the fact that not all cases of BMPR2 mutation develop PAH. Furthermore, the studies by Bauer et al. in mice subjected to acute hypoxia would also be consistent with a secondary role for TSP-1. Such a role, however, might be critical to the potentiation and perpetuation of PAH and might also contribute to the phenomenon of in situ thrombosis within the pulmonary circulation in patients with PAH.

The current study by Bauer et al. also does not examine the potentially interrelated impact of the endogenous NOS inhibitor asymmetric dimethylarginine (ADMA) as an additional source of eNOS 'uncoupling' in PAH. Plasma ADMA concentrations are substantially elevated in PAH and it is certainly possible that NOS uncoupling results from additive/synergistic effects of CD47 activation together with the ADMA effect and that the generation of superoxide (O$_2^-$) from 'uncoupled' eNOS might represent one component of the cause of sGC dysfunction in PAH. More remotely, it is also possible that TSP-1 might modulate with the BMPR2 axis via effects on TGF-β1 signalling. While the experimental data are compelling, means for treating PAH by clinical interruption of the TSP-1/CD47 axis are currently limited. The emerging interest in the utility of CD47 inhibitors should be accelerated by the current findings.

**Figure 1** Schematic view of potential interactions between TSP-1/CD47 and the NO/sGC signalling cascade: implications regarding the development of pulmonary hypertension. cGKI, cGMP-dependent protein kinase I; DDAH, dimethylarginine dimethylaminohydrolase. Other abbreviations are defined in the text.

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**References**


