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EDITORIAL

Protease-activated receptor 1 as potential therapeutic target in pulmonary arterial hypertension

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This editorial refers to 'Proteinase-activated receptor 1 antagonism ameliorates experimental pulmonary hypertension', by Y. Kuwabara *et al.*, pp. 1357–1368.

Pulmonary arterial hypertension (PAH) is a progressive disease of the pulmonary vasculature that is characterized by vasoconstriction and pulmonary vascular remodelling, as evidenced by intimal proliferation, medial hypertrophy, perivascular inflammation, and fibrosis. Endothelial dysfunction is thought to play a central role in these processes. Besides its role in maintaining vascular integrity and function, the endothelium provides a 'Teflon' coating of the vasculature with antithrombotic properties. Consistent with endothelial dysfunction in PAH, a pro-coagulant state exists in patients with PAH and autopsy studies have shown small thrombi in the pulmonary vasculature of patients with PAH.[1] Nevertheless, the Guidelines no longer recommend chronic anticoagulation for patients with PAH, because anticoagulation increases the risk for bleeding complications and microvascular thrombi are often considered an epi-phenomenon as there is no consensus as to whether microvascular thrombosis contributes to the pathogenesis of PAH.[2]

Despite this sceptical attitude, most studies do show a substantial survival benefit for patients with PAH treated with anticoagulation.[1–3] Furthermore, basic research supports the alternative hypothesis that activation of coagulation does contribute to microvascular lesion formation either by the fibrin clot itself, its pro-inflammatory properties, and/or through activation of proteases, tissue factor, factor Xa, and thrombin.[3] The intriguing part of this hypothesis is that the activated proteases of the coagulation cascade not only contribute to thrombus formation, but may also signal through so-called protease-activated receptors (PARs). These receptors are present on a variety of cell types, including endothelial cells, smooth muscle cells, fibroblasts, and inflammatory cells (*Figure 1*).[4] PAR1 expression is particularly high in the pulmonary vasculature, as compared to a variety of vessels from the systemic vasculature.[5] Moreover, activation of PAR1 induces vasoconstriction in the pulmonary vasculature,[6] promotes migration of pulmonary microvascular endothelial cells,[7] increased intracellular Ca^{2+} in pulmonary artery smooth muscle cells leading to increased smooth muscle cell proliferation (*Figure 1*).[8] This effect of PAR1 activation was more pronounced in smooth muscle cells derived from patients with PAH and chronic thrombo-embolic pulmonary hypertension (CTEPH).[8] Furthermore, PAR1 activation contributes to inflammatory cell recruitment and collagen deposition in response to lung-injury[9] and is involved in the development of endofibrotic lesions in the systemic vasculature.[10] Hence, PAR1-activation triggers processes that are critically involved in the development of PAH (*Figure 1*).

Kuwabara *et al.* show that, consistent with these findings, activation of PAR1 receptors in the intact pulmonary vasculature *in vitro*, using either thrombin or a specific PAR1 activating peptide, caused vasoconstriction that was more pronounced in lungs from rats with monocrotaline-induced PAH and was mediated by downstream activation of Rho-kinase. Moreover, they take these observations one step further and investigate whether PAR1 blockade with Atopaxar could alleviate PAH in a rat model of monocrotaline-induced PAH.[5] Indeed, Ataxopar improved survival in PAH-rats, albeit more in a preventive treatment strategy, starting prior to induction of PAH than in a reversal strategy starting treatment when PAH was already established. These beneficial effects on survival were accompanied by a reduction in medial wall thickness of the pulmonary small arterioles. To further establish a role for PAR1 in pulmonary vascular remodelling, $PAR1^{-/-}$ mice were exposed to chronic hypoxia. Also, in this model, loss of PAR1 activity reduced severity of pulmonary vascular remodelling and pulmonary hypertension (PH). Together with the observation that PAR1 is highly expressed in the thrombi of patients with CTEPH,[8] these data suggest that PAR1 activation may be one of the underlying mechanisms responsible for the arteriopathy in PAH and CTEPH and may play a detrimental role in development of different types of PH.

In accordance with its beneficial effect on the pulmonary vasculature, resulting in a reduced pulmonary vascular resistance and hence right ventricular (RV) afterload, $PAR1^{-/-}$ also reduced RV hypertrophy. However, in addition to these 'indirect' effects of PAR1 on the heart, PAR1 expression is also present on cardiomyocytes and (myo)fibroblasts, and hence PAR1-inhibition can also directly influence cardiac remodelling (*Figure 1*). Thus, PAR1 inhibition reduced thrombin-induced proliferation[11] and hypertrophy[12] of cardiomyocytes and reduced left ventricular remodelling and interstitial fibrosis in response to diabetes[13] and myocardial infarction.[14,15] Hence, in addition to attenuating pulmonary vascular remodelling, PAR1 blockade may also directly impact RV

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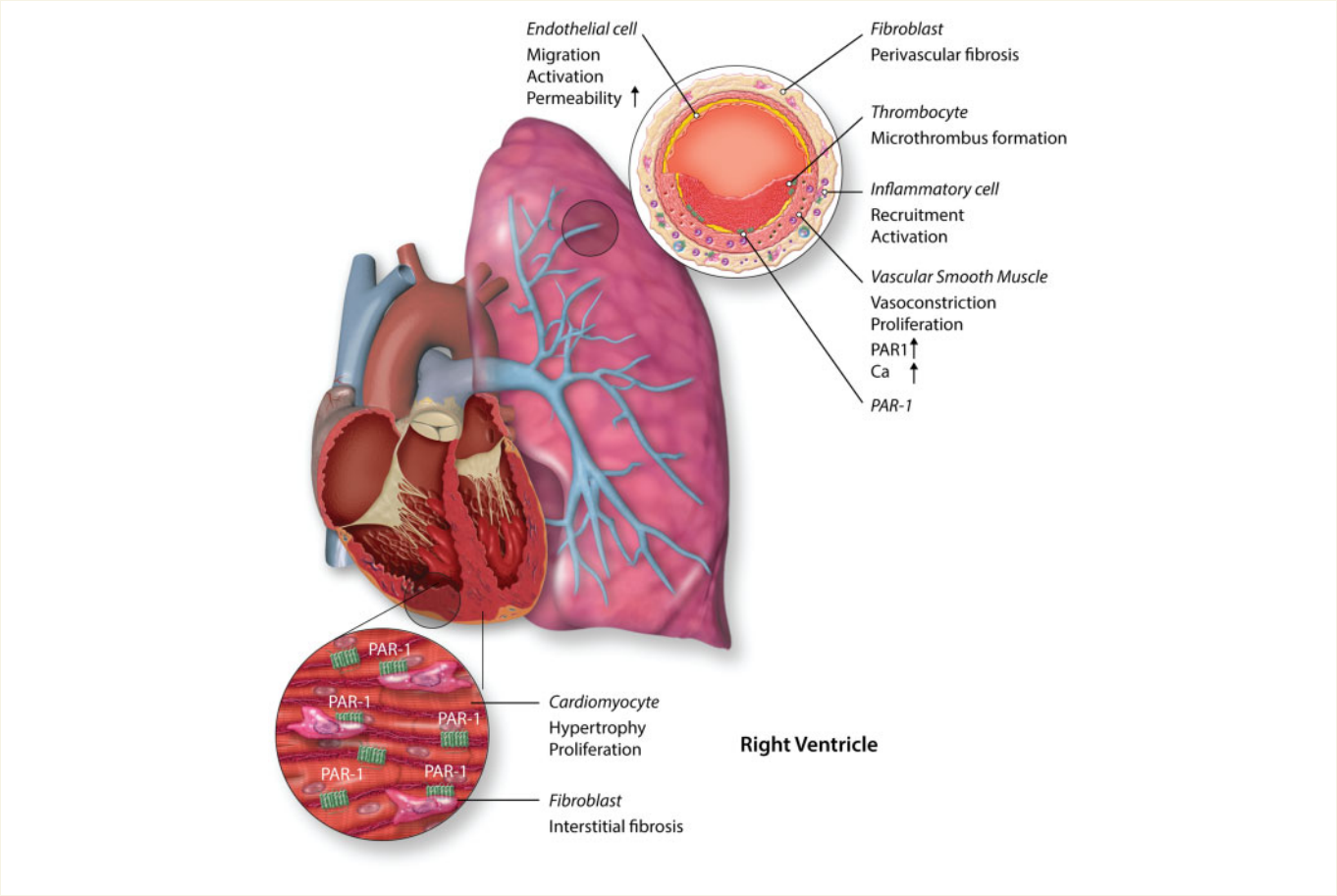

Figure 1 The Protease Activated Receptor 1 (PAR1) is expressed on multiple cell types both in the pulmonary vasculature and the right ventricle. Activation of PAR1 plays a role in processes involved in development and progression of pulmonary hypertension as outlined in the figure, suggesting that interfering with PAR1 activation may provide a novel therapeutic target for pulmonary hypertension.

hypertrophy, remodelling, and fibrosis. Although some degree of RV hypertrophy is required to cope with the increased afterload in PAH, RV remodelling, and particularly interstitial fibrosis negatively impact RV function and predispose to RV failure in patients with PAH.

Future research should evaluate whether PAR1 blockade can also attenuate RV remodelling in response to pressure-overload while maintaining RV function. Furthermore, it should be evaluated if PAR1-blockade is associated with less bleeding risk than conventional anticoagulation with warfarin. If this is the case, PAR1 blockade may be a valuable addition to the therapeutic armamentarium for patients with PAH, CTEPH, as well as PH associated with hypoxia.

Conflict of interest: none declared.

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