Pulmonary arterial hypertension (PAH) is a life-threatening syndrome resulting from restricted pulmonary arterial circulation, which leads to a pathological increase in pulmonary vascular resistance (PVR) and ultimately to right heart failure. Multiple pathogenic factors causing the imbalance in homeostasis between vasoconstriction and vasodilatation, and the imbalance of cell proliferation and apoptosis, have been implicated in the development of PAH. Although progression of the disease is still inevitable, there has been advances in basic and clinical research throughout the past decade. With increasing insight into the pathology of PAH, the disease has also attracted considerable interest in drug development in recent years. Based on the evidence from prospective randomized clinical trials, 3 main strategies (administration of prostacyclin, antagonism of endothelin receptors, and inhibition of phosphodiesterase-type 5 (PDE5)) represent the current first-line treatments. Compared with the conventional therapeutic management of PAH, these agents have a positive effect on the course of the disease and improve patient outcomes. Furthermore, basic studies have identified several future therapeutic targets, such as tyrosine kinase, soluble guanylate cyclase, vasoactive intestinal peptide and 5-HT transporter (5-HTT). Added to these, Rho-kinase has become an important target for the treatment of PAH.

Activation of RhoA/Rho-kinase signaling plays a key role in the regulation of pulmonary vascular tone, which modifies the Ca\(^{2+}\)-sensitivity of smooth muscle cell (SMC) contraction by inhibiting myosin light chain (MLC) phosphatase and enhancing MLC phosphorylation.

Many basic studies have demonstrated the involvement of Rho-kinase activation in the pathogenesis of PAH. Hypoxia activates Rho-kinase in SMCs and causes vasoconstriction. In vivo, a link between 5-HTT and RhoA activation has been demonstrated in the pulmonary arteries of rats under hypoxic conditions. When 5-HT is internalized in vascular SMCs through 5-HTT, it is covalently linked to RhoA by intracellular type 2 transglutaminase, leading to constitutive RhoA activation.

Nitric oxide-induced relaxation and endothelin-1-induced vasoconstriction of pulmonary arteries are also mediated in part by Rho-kinase-mediated Ca\(^{2+}\)-sensitisation. With the development of specific inhibitors of Rho-kinase, such as Y-27632 and fasudil, the role of Rho-kinase in the development of PAH has been clarified. Rho-kinase inhibitors completely normalized PVR in a rat model of newborn persistent PH. Acute hypoxic pulmonary vasoconstriction and hypoxic PH in mice were ameliorated by inhibition of Rho-kinase. Long-term inhibition of Rho-kinase with fasudil attenuates monocrotaline-induced PAH in rats.

The protective effects of sildenafil in hypoxia- and bleomycin-induced PH are also mediated by the phosphorylation of RhoA and prevention of its translocation to the plasma membrane. Furthermore, the combination of prostacyclin and fasudil leads to a greater improvement in monocrotaline-induced PH in rats than did treatment with either prostacyclin or fasudil alone. Several animal studies have shown protective effects of HMG-CoA reductase inhibitors (statins) on PAH development. Some of the pleiotropic effects of statins are also mediated through the inhibition of Rho-kinase by the isoprenoids farnesyl and geranylgeranyl pyrophosphate, which are intermediates in the production of cholesterol.

Although low intravenous doses of fasudil rapidly cause modest decreases in PVR and mean pulmonary artery pressure (mPAP) in patients with PAH, with reductions in systemic vascular resistance and systolic systemic arterial pressure, clinical studies of RhoA/Rho-kinase signaling in human PAH are still limited. Moreover, direct evidence linking the findings from basic studies to outcomes in clinical studies is lacking.

In this issue of the Journal, Zhulanqiqige et al report Rho-kinase activation in both circulating neutrophils and lung tissue of patients with PAH. Their findings appear to provide direct evidence for Rho-kinase activation in PAH patients. Interestingly, the Rho-kinase activation was not only localized in lung tissue, but also present systemically. Rho-kinase activity in circulating neutrophils correlated well with mPAP and the duration of the disorder. With progression of PAH, right ventricular function worsens while mPAP is unchanged or may decrease. In patients with PAH, the mPAP has less prognostic value than the mean right atrial pressure and the cardiac index. Because the study by Zhulanqiqige et al revealed no significant correlation between Rho-kinase activity and either cardiac index or right atrial pressure, Rho-kinase activation may not be...
directly linked to the severity of the disorder. Although the underlying mechanism of Rho-kinase activation in circulating neutrophils of PAH patients is unclear, the authors speculate that Rho-kinase in circulating neutrophils is activated when the neutrophils pass through the lungs. It is reasonable that Rho-kinase activation in the pulmonary vasculature is a pathogenic upstream signal that causes pulmonary vasoconstriction and remodeling in PAH. However, PAH itself may also activate Rho-kinase in lung tissue with the affecting cells in the systemic circulation, which may form a positive feedback loop that worsens the PAH. Furthermore, systemic activation of Rho-kinase in circulating cells may modulate cell adhesion and inflammatory responses, which would also form a local (pulmonary)–systemic feedback loop, further exacerbating PAH. Another finding of this study was impaired endothelial vasodilator function and hypercontraction of vascular smooth muscle cells (VSMCs) in isolated pulmonary arteries from patients with PAH. The hypercontraction of VSMCs was abolished by inhibition of Rho-kinase. These results provide a scientifically logical basis to encourage clinical trials examining the efficacy and safety of Rho-kinase inhibitors for the treatment of PAH.

The Rho-kinase inhibitor, fasudil, was approved in 1995 in Japan as an agent for the treatment of vasospasm after arachnoidal hemorrhage. Rho-kinase-mediated alterations are thought to be involved in various cardiovascular disorders including PAH, arteriosclerosis and vasospastic angina. A clinical trial examining the effectiveness and safety of oral administration of fasudil in patients with PAH is now under way. Further studies are necessary to address issues of the long-term safety and efficacy of Rho-kinase inhibitors, as well as its synergistic effects with other treatment entities such as prostacyclin analogs, PDE5 inhibitors and endothelin receptor antagonists.

References


