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Editorial

New Therapeutic Target for Pulmonary Arterial Hypertension

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▸ See the article "Protective Effect of Right Ventricular Mitochondrial Damage by Cyclosporine A in Monocrotaline-induced Pulmonary Hypertension" in volume 48 on page 1135.

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Currently, the therapies for pulmonary arterial hypertension (PAH) such as endothelin receptor antagonists (ERAs) which target endothelin pathway, phosphodiesterase type 5 inhibitors (PDE-5is) which target nitric oxide pathway, and prostacyclin analogues which target prostacyclin (PGI_2) pathway either alone or in combination, are considered primary treatments. These improve functional capacity of patients but not the survival.

Novel therapeutic strategies and newer agents are needed to target multiple pathways involved in vasoconstriction, cellular proliferation, the inflammatory response, and so on. Recently, several other therapeutic agents have been suggested.

Rho kinase inhibitors, vasodilator peptides (vasoactive intestinal peptide, adrenomedullin), and endothelial nitric oxide synthase coupling agents (cicletanine) showed to exert potent pulmonary vasodilatory effects in animal models and in pilot studies in humans. Tyrosine kinase inhibitors (platelet-derived growth factor, epidermal growth factor receptor inhibitors), elastase inhibitors, survivin inhibitors, and HMG-COA reductase inhibitors have been shown to reverse pulmonary hypertension in rodent models of pulmonary hypertension through inhibition of cell proliferation and induction of apoptosis. Furthermore, anti-inflammatory or immunomodulatory agents (thiazolidinedinones, rapamycin, cyclosporine, and STAT3 inhibitors) have been demonstrated to be effective at reducing vascular remodeling in animal models.[1)]

Endothelial cell mitochondria are considered signaling organelles that modulate the angiogenic process or supply biosynthetic molecules, although the mechanism is uncertain. Mitochondrial permeability transition pore (MPTP) may be involved to manipulate angiogenesis. MPTP activation terminates mitochondrial function and triggers cell death. The mitochondrial matrix protein cyclophilin D, which is encoded by the nuclear gene Ppif and inhibited by cyclosporineA (CsA), is a key regulator of Ca^{2+}-induced MPTP opening. The mitochondrial regulation of silent information regulator 1 (SIRT1) has broad implications in the epigenetic regulation of endothelial phenotype.[2)]

Then, can we apply this MPTP model in myocardial ischemia-reperfusion injury to that in PAH model?[3)] There are few reports that MPTP is associated with PAH in both vitro and

vivo. Rev (Rev, 3,5,4-trihydroxystilbene), a polyphenol isolated from grapes and polygonum cuspidatum, has been shown to possess antioxidative properties. It produced a beneficial effect partially by enhancing the activation of SIRT1, thus improving RVSP and reducing RVH. SIRT1 activation increased PASMC apoptosis in a dose-dependent manner in vitro by inducing mPT dysfunction, which might be a novel future strategy for the treatment of PAH.

Chronic hypoxia-induced PAH is a life-threatening disease that is characterized by progressive remodelling of the pulmonary vasculature, which can ultimately lead to right heart failure and death. The hallmark of terminal PAH is the development of plexiform lesions resulting from the excessive proliferation and migration of pulmonary artery endothelial cells and pulmonary artery smooth muscle cells. Although there are several current therapeutic agents, novel therapeutic strategies and newer agents are needed to target multiple pathways involved in vasoconstriction, cellular proliferation, the inflammatory response.[4] CsA efficiently inhibited compression-induced nucleus pulposus mesenchymal stem cells apoptosis by alleviating mitochondrial dysfunction and oxidative stress.[5]

In a recent study to evaluate protective effects of CsA which is one of MPTP blockers, CsA reduced RV mitochondrial damage in monocrotaline (MCT)-induced PAH models. They described CsA is an important factor to prevent MCT-induced myocardial damage of PAH by reducing caspase-3 expression. Oxidative stress followed by calcium overload, ATP depletion may induce MPTP opening, which results in mitochondrial swelling, rupture, and cell death.[6]

This is a very interesting study since there are few reports that dealing with prevention of RV failure other than regression of pulmonary vascular disease. CsA can be one of the options to prevent RV damage in patients with PAH treating with conventional treatment.

However, this results are just in animal model. Additionally, application of dose-dependent effect of CsA on RH function as well as more validated study will be needed to apply to human.[6]

Recent similar study described that the injection of human umbilical cord blood derived mesenchymal stem cells improved inflammation, apoptosis and remodeling in the lung/heart tissues of MCT-induced PAH mouse model.[7]

But, there is single report that CsA-induced PAH through the mechanism of endothelial injury affecting endothelial nitric oxide function results in smooth muscle cell proliferation and PAH.[8]

In clinical practice, combination therapy is regarded as the standard. In majority, patients are treated with ERA combined with PDA-5is. PGI_2 pathway inhibitors are frequently added in severe PAH patients. In AMBITION study, edema and headache occurred more frequently in patients with combination of ambrisentan and tadalafil compared with monotherapy with either drug. The tolerability of sequential combination therapy than initial combination therapy is supported by SERAPHIN trial, in which macitentan, 64% of PAH patients receiving at baseline therapy, was well-tolerated.

The long-term GRIPHON study provided evidence of randomized controlled trial of triple combination therapy for the first time, including selexipeg (oral selective IP prostacyclin receptor agonist) in addition to double combination therapy.

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In PAH patients with underlying disease, comorbidities should be considered for selecting treatment regimens. In patients with coronary artery disease using nitrates, co-administration with PDE-5is is contraindicated due to serious additive hypotensive effect. In patients with type 2 diabetes treated with glucose-lowering glyburide, co-administration of bosentan resulted in reduced plasma levels of both drugs. In REACH-1 trial of patients with chronic heart failure, because of increased incidence of elevated liver enzymes in patients with bosentan and glyburide, co-administration is contraindicated. In patients with human immunodeficiency virus treated with anti-retroviral drugs that are strong CYP3A4 inhibitors, which can interfere with ERAs and PDA-5is metabolism. PAH patients with associated connective tissue disease, who may receive immunosuppressant, co-administration of bosentan with cyclosporine is contraindicated.[9]

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