Pulmonary hypertension (PHTN) remains a disease with high morbidity and mortality and no known cure. The World Health Organization has categorized PHTN into 5 clinical classifications, as follows: (1) pulmonary artery hypertension; (2) PHTN with left heart disease; (3) PHTN with respiratory disease; (4) PHTN caused by chronic thrombotic/embolic disease; and (5) miscellaneous PHTN. Despite the broad and varied nature of these clinical conditions, PHTN presents with similar clinical pathological changes in the lung, including altered vasoreactivity, endothelial dysfunction, vascular intimal and medial remodeling, activation of inflammatory processes, and platelet activation. If untreated, these changes lead to right heart stress, failure, and death. At the cellular level, enhanced vasoconstriction, endothelial dysfunction, and endothelial cell and vascular smooth muscle cell (VSMC) proliferation are key components of disease progression. This underlying pathology is associated with a plethora of molecular changes, eg, increased inflammatory cytokine expression and increased levels of oxidative stress, altered NO bioavailability, and increased growth factor expression. These molecular changes alter the balance of kinase cascades, cAMP, cGMP, and rho that ultimately modulate K⁺ and Ca²⁺ channel function and expression, cytoskeletal organization, and cell cycle progression.

Current treatment targets for PHTN include Ca²⁺ channel blockade, selective endothelin A receptor and dual endothelin receptor antagonist, prostanoid replacement, and phosphodiesterase inhibition. These treatments may be applied singularly or in combination to achieve therapeutic goals. Moreover, these therapies have had limited success and are often associated with unwanted adverse effects, including systemic hypotension. The rapid rate of drug discovery for this condition is somewhat reassuring, but finding a single drug therapy that targets the numerous pathological changes in PHTN, free of adverse effects, is less plausible.

Over the past 2 decades, increasing attention has been given to red wine polyphenol, resveratrol (3,5,4’-trihydroxystilbene), a dietary phytalexin compound. This is attributed in part to its cardioprotective, vasoactive, and anticancer properties. This compound is capable of acting as a pleiotropic agent in antioxidant, anti-inflammatory, antiproliferative, and antifibrotic capacities. More recently, resveratrol has attracted interest as a novel, therapeutic approach for the prevention and treatment of multiple cardiovascular diseases, including atherosclerosis and ischemia/reperfusion injury. Importantly, the multiple actions attributed to resveratrol on the systemic and cardiac vasculature may also target the mediators of pulmonary hypertensive diseases.

In the present issue of Hypertension, Csiszar et al are the first to demonstrate the remarkable efficacy of resveratrol in preventing the pulmonary and cardiac abnormalities in a rat model of PHTN induced by monocrotaline (MCT). MCT is a toxic pyrrolizidine alkaloid, and administration of a small MCT dose or its active metabolite, MCT pyrrole, to rats causes a delayed and progressive lung injury, which is characterized by endothelial cell dysfunction, pulmonary vascular remodeling, PHTN, and right ventricular hypertrophy. Treatment with resveratrol (25 mg/kg per day started on the day of MCT administration) prevented these changes. The actions of resveratrol were attributed, in part, to reduced pulmonary VSMC proliferation, increased endothelial NO synthase and NO bioavailability, reduced oxidative stress, decreased inflammatory cytokine levels, and decreased lung leukocyte infiltrate and inducible NO synthase levels (Figure). At the molecular level, transforming growth factor-β and tumor necrosis factor-α levels were normalized, NOX subunits of the NADPH oxidase were reduced, and endothelial NO synthase levels were increased.

Despite the intriguing findings presented in this article, a number of questions remain to be elucidated (Figure). For example, how does resveratrol affect ion channels, which are important in pulmonary vascular constriction and VSMC proliferation? Potential targets are membrane-associated ion channels, in particular K⁺ and Ca²⁺ channels that play a large role in modulating pulmonary vasomotor tone and pulmonary artery VSMC proliferation in acute and chronic hypoxic states. Under chronic hypoxic conditions, voltage-activated K⁺ channels and voltage-independent Ca²⁺ channels modulate the increase in chronic pulmonary vasoconstriction, whereas the resulting sustained increase in intracellular Ca²⁺ stimulates pulmonary artery VSMC proliferation. The effects of resveratrol on these channels in MCT-induced PHTN require further study. Interestingly, one might speculate that changes in channel activity could affect both pulmonary arterial smooth muscle cell constriction and proliferation. Furthermore, resveratrol has also been shown to induce smooth muscle relaxation in a number of human and animal vascular beds. In these studies, resveratrol was shown to affect large-conductance Ca²⁺ and voltage-activated K⁺ channels. These channels are key regulators of pulmonary arterial tone, and their inhibition has been implicated in the development of PHTN.
Resveratrol also antagonizes the activation of a number of molecular pathways that underlie the proinflammatory and proliferative responses to MCT. Resveratrol inhibits the activation of CREB, c-jun, AP-1, and nuclear factor κB (NF-κB) transcription factors. In particular, downregulation of NF-κB, AP-1, and extracellular signal–regulated kinase activity by resveratrol is associated with many of its observed antioxidative, anti-inflammatory, and antiproliferative effects. Recent studies have verified a link between resveratrol-mediated NF-κB inhibition and AP-1 inhibition in smooth muscle cells. NF-κB blockade may be secondary to inhibitory kappa B (IkB) kinase inhibition, preventing NF-κB translocation to the nucleus. Studies performed by Son et al. independently demonstrated that resveratrol decreased proinflammatory cytokine transcriptional profiles via inhibition of NF-κB and AP-1 activity when cells were challenged with tumor necrosis factor-α and lipopolysaccharide, respectively. Resveratrol also elicits anti-inflammatory effects by decreasing NF-κB–mediated lung neutrophil infiltration. In addition, resveratrol has been shown to dose-dependently arrest aortic VSMCs in the G1 phase of the cell cycle. Reduced extracellular signal–regulated kinase-MAPK signaling is also thought to play a role in decreasing cyclin-dependent kinase levels, resulting in a cessation of the cell cycle of VSMCs.

In the present study by Csiszar et al., resveratrol induced an antiproliferative response in pulmonary VSMCs that was associated with S-phase cell-cycle arrest.

Another remaining question is whether resveratrol independently targets multiple processes that contribute to the above findings or whether there is an integral element that accounts for these pleiotropic actions. It is tempting to speculate that reactive oxygen species scavenging may be at the center of the diverse actions of resveratrol. Increased oxidant stress plays a major role in vasoconstriction, NO bioavailability, cell proliferation, and inflammation in pulmonary endothelial cells and VSMCs. In addition to directly scavenging reactive oxygen species, resveratrol also increases the expression of a number of antioxidant enzymes, eg, glutathione, peroxidase, catalase, and heme-oxidase 1 in aortic vessels, but these changes have not been documented in the pulmonary vasculature. Additional work is needed to disentangle the relative importance of each of these contributing factors.

Although MCT treatment is one of several models of PHTN, questions remain regarding the efficacy of resveratrol in other models of PHTN that encompass more severe pathophysiology or in distinctly different PHTN models (ie, chronic hypoxia exposure, early ductus arteriosus ligation, chronic embolic delivery, and others). Moreover, it is unclear whether resveratrol can reverse or attenuate established PHTN, an important clinical goal. Another area of needed study involves sex differences in PHTN, because resveratrol exerts antiproliferative effects in aortic VSMCs by binding to estrogen receptors, implying sex-specific alterations in activity. Finally, the effects of resveratrol on developmental models of PHTN need to be studied, because these models demonstrate pathophysiologic differences.

In summary, the authors make a convincing argument for multiple beneficial effects of resveratrol on MCT-induced PHTN in adult rats. However, additional preclinical studies followed by clinical trials are needed before resveratrol can be considered the magic bullet for PHTN.

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