eNOS uncoupling in pulmonary hypertension

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Online publish-ahead-of-print 13 October 2011

This editorial refers to ‘Pulmonary hypertension in adult Alk1 heterozygous mice due to oxidative stress’ by M. Jerkic et al., pp. 375–384, this issue.

Pulmonary arterial hypertension (PAH) is characterized by high blood pressure and vascular remodelling in pulmonary arteries and subsequently right ventricular hypertrophy. Although several studies in animal models of pulmonary hypertension (PH) and pathological examinations of lung tissue obtained from PAH patients show occlusion of pulmonary arteries, the exact molecular mechanisms for vascular abnormalities remain unclear. Endothelial dysfunction seems to be one of the earliest events in PAH and is characterized by reduced levels of vasodilators nitric oxide (NO) and prostacyclin and increased vasoconstrictor agents, such as endothelin-1 and prostanoids. NO formed from L-arginine by endothelial nitric oxide synthase (eNOS) plays an important protective role in vascular haemostasis.

Activin receptor-like kinase 1 (Alk1) is a type I receptor of transforming growth factor-beta family proteins or bone morphogenetic proteins and is mainly expressed in endothelial cells, regulating proliferation and migration in vitro and angiogenesis in vivo. Mutation of the Alk1 gene causes hereditary haemorrhagic telangiectasia type II in patients, an autosomal dominant vascular dysplasia that results in abnormal blood vessel formation in the skin, mucous membranes, and often in organs such as the lungs, liver, and brain, suggesting that Alk1 may play an important role during vascular development. Jerkic et al. showed that deletion of one copy of the Alk1 gene (Alk1+/−) caused PAH in adult mice as characterized by increased right ventricular systolic pressure, vascular remodelling, decreased vascular density, and endothelial dysfunction of pulmonary arteries. In contrast, no signs of endothelial dysfunction and PAH were detected in young Alk1+/− mice. The authors identified increased production of oxygen-derived species (ROS) including superoxide anion (H2O2) in the lungs of adult but not newborn Alk1+/− mice. Remarkably, endothelium-dependent relaxation to acetylcholine was enhanced in pulmonary arteries of adult Alk1+/− mice despite reduced production of NO. Dysfunction of eNOS in endothelial cells can be an important source for production of H2O2, which is a potent vasodilator that activates soluble guanylate cyclase and elevates levels of cyclic guanosine monophosphate in vascular smooth muscle cells. Studies with an NOS inhibitor suggested that eNOS-catalysed formation of superoxide anion and subsequent formation of H2O2 may represent an important mechanism underlying endothelial dysfunction described in a number of vascular diseases.

Furthermore, the authors elegantly showed that in vivo treatment with the cell-permeable superoxide dismutase mimetic tempol completely prevented characteristic signs of PAH in Alk1+/− mice despite increased levels of H2O2, indicating that superoxide anion is a mediator of PH. The role of superoxide anion in several forms of PAH has been demonstrated in previous studies. There are several sources of superoxide anion in vascular endothelium, for example, increased activity of NADPH oxidase, xanthine oxidase, and/or cyclooxygenase. In addition, reduced antioxidant defence capacity and/or impaired enzymatic activity of eNOS may contribute to elevation of superoxide anion concentration and subsequent endothelial dysfunction. In the present study, however, no differences in protein expression of enzymes involved in ROS generation and scavenging were found between wild-type and Alk1+/− mice.

Since phosphorylation of eNOS is a key posttranslational modification that ensures optimal production of NO, increased basal phosphorylation of eNOS at Ser1177 and uncoupling of eNOS as a source of superoxide anion were identified in the lungs of Alk1+/− mice. It is well established that tetrahydrobiopterin (BH4) is an essential cofactor for allosteric and redox activation of eNOS and that BH4 is mainly produced in the vascular endothelium. Several biochemical studies have demonstrated that suboptimal concentrations of BH4 result in the generation of superoxide anion by eNOS. Furthermore, in intact blood vessels depleted of BH4, eNOS may become a source of ROS in vivo. During chronic eNOS activation, BH4 can also become deficient, leading to the production of superoxide anion by eNOS. Importantly, the authors provide no BH4 data to suggest that increased oxidation of BH4 and/or decreased BH4 biosynthesis via GTP-cyclohydrolase I causes eNOS uncoupling. However, two prior independent studies have demonstrated that BH4 deficiency causes PH in vivo even under normoxic conditions. Moreover, selective augmentation of endothelial BH4 biosynthesis protects vascular wall against increased production of superoxide anion caused by uncoupling of eNOS and thus prevents PH in BH4-deficient hph-1 mice. It would be important to investigate whether PH and increased release of superoxide anion and H2O2 from eNOS can be prevented by BH4 treatment in Alk1+/− mice.

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It is also interesting to note that Alk1 is located in endothelial caveolae along with eNOS where both functionally interact with caveolin-1 through its scaffolding domain. Selective suppression of caveolin-1 abrogated the Alk1 signalling pathway in endothelial cells. Furthermore, studies with caveolin-1-deficient mice revealed chronic up-regulation of eNOS activity, leading to development of PAH. Consistent with a role for eNOS uncoupling in the pathogenesis of PH, deletion of the eNOS gene prevents pulmonary vascular remodelling and the PH phenotype in caveolin-1-deficient mice.

In conclusion, Jerkic et al. indicated that deletion of a single copy of the Alk1 gene can cause eNOS uncoupling, oxidative stress, and subsequent development of PAH. The beneficial effects of antioxidant therapy in this genetic model of PAH suggest an interesting alternative for the prevention of PAH in humans.

Conflict of interest: none declared.

References