submit

Member Login:

submit

Forgot Password? | Register for an Account

Advances in PH Journal

Pathogenesis of Pulmonary Arterial Hypertension: Clues From Patient and Animal Models of Hereditary Hemorrhagic Telangiectasia

Mourad Toporsian

//

Reviews

Sign in to add a review

0 comments
Leave a Comment

Vol 11, No 3 (Fall 2012)

- Toporsian, M. Pathogenesis of PAH: Clues From Patients and Animal Models of Hereditary Hemorrhagic Telangiectasia. *Advances in Pulmonary Hypertension.* 2012;11:3: 128-129.

Download This Issue

Download This Article

Hereditary hemorrhagic telangiectasia (HHT) is a vascular disease characterized by multiple focal telangiectases and arteriovenous malformations (AVMs) in the pulmonary, hepatic, and cerebral microcirculations. These fragile structures are low-pressure conduits that can affect local tissue blood flow, and their potential rupture in vital organs can lead to internal hemorrhage, anemia, and death. Patients with HHT1 and HHT2 display very similar vascular lesions, but diverge with respect to organ involvement, where a higher prevalence of pulmonary AVMs (PAVMs) is seen in HHT1.[1]

Mutations in the endoglin (ENG) and activin-like kinase 1 receptor (ACVLR1, ALK1) genes leading to haploinsufficiency are the underlying causes of HHT type 1 and HHT type 2,

respectively. Recent findings indicate that individuals harboring mutations in ENG or ACVLR1 can also present with varying degrees of pulmonary arterial hypertension (PAH) and/or HHT, suggesting that these diseases share defects in common or related signaling pathways. ENG is a 180kD homodimeric transmembrane glycoprotein that is mostly expressed on endothelial cells and acts as an ancillary receptor for several transforming growth factor-beta (TGF-?) superfamily ligands, including bone morphogenetic proteins (BMPs).[2] It can be found in both TGF-? and BMP receptor complexes such as TGF-? receptor 2 (T_RII)/ALK1[3] and BMPR2/ALK1.[4] ENG physically interacts with ALK1 and regulates its activity[3] within these complexes. Both ENG-null ($ENG^{-/-}$)[5,6] and ALK1-null (ALK1-/-)[7] mice die at mid-gestation (E9.5) from severe cardiovascular defects, while heterozygous mice are viable and serve as valuable models to study HHT.

In PAH, endothelial dysfunction and the characteristic loss of peripheral capillaries are believed to precede the muscularization and remodeling of pulmonary arteries.8 The activity of the endothelial nitric oxide synthase (eNOS) and nitric oxide (NO•) bioavailability are critical determinants of normal endothelial and vascular function, which are perturbed in patients with PAH and in many animal models of this disease.[9-11] For example, eNOS activity is reduced in hypoxiainduced pulmonary hypertension as a result of impaired association of eNOS with its allosteric activator, heat shock protein 90 (Hsp90).[12] These changes in eNOS activation lead to increased eNOS-derived reactive oxygen species (ROS) production instead of NO• in endothelial cells,[13] and have been observed in an animal model of persistent pulmonary hypertension of the newborn.14,15 In response to a stimulus, eNOS activity is termed uncoupled when eNOS fails to efficiently couple the conversion of its substrate, L-arginine, to NO• and instead produces superoxide (•O2 -; generally measured as ROS). Conditions that cause eNOS uncoupling include: 1) substrate (L-arginine) and/or co-factor (tetrahydrobiopterin, BH4) deficiencies, and 2) the impaired ability of eNOS to bind Hsp90.

ENG and ALK1 are expressed on endothelial cells of the distal pulmonary vasculature.[16] ENG resides in endothelial caveolae, associates with eNOS, and facilitates eNOS activation by acting as a scaffolding protein, bringing cytoplasmic Hsp90 into close proximity with caveolar eNOS, and thus resulting in normal NO• production. ENG-deficient endothelial cells have reduced eNOS/Hsp90 association during agonist-induced activation and produce increased eNOS-derived ROS instead of NO•.[17] Interestingly, adult $ENG^{+/-}$ mice spontaneously acquire signs of PAH, including increased right ventricular systolic pressure (RVSP), muscularization of pulmonary arteries, and pruning of distal vessels.[18] The onset of PAH in these mice is developmentally regulated and due to uncoupled eNOS activity acquired in adulthood.[18,19] Treatment of adolescent ENG_/- mice with the antioxidant Tempol prevents the onset and progression of PAH. More recently, it has been shown that adult $ALK1^{+/-}$ mice also acquire signs of PAH due to uncoupled eNOS activity,[20] providing further support that a common defective pathway involving ENG/ALK1/eNOS may be critical for the spontaneous onset and progression of PAH. More specifically, ENG links TGF-?/BMP receptors including ALK1 to the eNOS activation complex. Its reduction renders eNOS unresponsive to the regulation of its phosphorylation status by TGF-?/BMP signals, leading to constitutive endothelial eNOS-derived oxidative stress.[18,20]

While both $ENG^{+/-}$ and $ALK1^{+/-}$ mice acquire signs of PAH in adulthood via similar mechanims,[18,20] it is important to note that $ALK1^{+/-}$ mice display a more severe phenotype. This has also been observed in humans harboring ALK1 mutations who tend to have a greater prevalence and severity of PAH compared to those with ENG mutations. Interestingly, PAVMs are more prevalent in HHT1(ENG mutation) than in HHT2 (ALK1mutation) patients

(48% vs 5%).[1] These low-resistance structures may serve to alleviate overall pulmonary vascular resistance (PVR) and thus mask the severity and attenuate the progression of PAH in patients with ENG mutations.[21] Indeed, patients with ENG mutations presenting with PAH typically have lower PVR than those with ALK1 mutations.[4] Moreover, in some of these cases, the increased pulmonary arterial pressure has eventually normalized with the appearance of PAVMs.[22,23] These studies suggest that ENG mutations are a predisposing factor to PAH, and that PAVMs in HHT1 may result from abnormal vascular remodeling under high local pressure conditions, which may in turn serve to alleviate PVR. Manifestations of PAH and/or HHT may be influenced by genetic and environmental modifying factors that specifically affect the integrity of the $ENG^{+/-}$ pulmonary vasculature and its ability for normal remodeling/repair under elevated intravascular pressure.

In summary, TGF-?/BMP signaling and eNOS activity are critical determinants of normal endothelial function and survival, which may be perturbed in PAH patients and in many animal models of this disease. ENG links certain TGF-?/BMP receptors to the eNOS activation complex, and that adult $ENG^{+/-}$ and $ALK1^{+/-}$ mice spontaneously develop signs of PAH due to increased pulmonary endothelial oxidative stress and reduced NO• bioavailability. A growing number of studies suggest a close association between PAH and HHT, and current experimental systems may provide a means to define the specific determinants in the pathogenesis of AVMs from those that underpin vascular remodeling leading to PAH. Moreover, the identification of novel factors that can regulate the level/activity of ENG, ALK1, and their associated signaling pathways irrespective of inborn mutations in TGF-?/BMP receptors may represent novel biomarkers of disease and potential therapeutic targets in the onset and progression of PAH.

References

1. Letteboer TG, Mager JJ, Snijder RJ, et al. Genotype-phenotype relationship in hereditary haemorrhagic telangiectasia. *J Med Genet.* 2006;43(4): 371-377.
2. Barbara NP, Wrana JL, Letarte M. Endoglin is an accessory protein that interacts with the signaling receptor complex of multiple members of the transforming growth factor-beta superfamily. *J Biol Chem.* 1999;274(2):584-594.
3. Blanco FJ, Santibanez JF, Guerrero-Esteo M, Langa C, Vary CP, Bernabeu C. Interaction and functional interplay between endoglin and ALK-1, two components of the endothelial transforming growth factor-beta receptor complex. *J Cell Physiol.* 2005;204(2):574-584.
4. David L, Mallet C, Mazerbourg S, Feige JJ, Bailly S. Identification of BMP9 and BMP10 as functional activators of the orphan activin receptorlike kinase 1 (ALK1) in endothelial cells. *Blood.* 2007;109(5):1953-1961.
5. Bourdeau A, Dumont DJ, Letarte M. A murine model of hereditary hemorrhagic telangiectasia. *J Clin Invest.* 1999;104(10):1343-1351.
6. Li DY, Sorensen LK, Brooke BS, et al. Defective angiogenesis in mice lacking endoglin. *Science.* 1999;284(5419):1534-1537.
7. Oh SP, Seki T, Goss KA, et al. Activin receptorlike kinase 1 modulates transforming growth factorbeta 1 signaling in the regulation of angiogenesis. *Proc Natl Acad Sci U S A.* 2000;97(6):2626-2631.
8. Rabinovitch M. Molecular pathogenesis of pulmonary arterial hypertension. *J Clin Invest.* 2008; 118(7):2372-2379.

9. Farber HW, Loscalzo J. Pulmonary arterial hypertension. *N Engl J Med.* 2004;351(16):1655-1665.
10. Grobe AC, Wells SM, Benavidez E, et al. Increased oxidative stress in lambs with increased pulmonary blood flow and pulmonary hypertension: role of NADPH oxidase and endothelial NO synthase. *Am J Physiol Lung Cell Mol Physiol.* 2006; 290(6):L1069-L1077.
11. Wunderlich C, Schmeisser A, Heerwagen C, et al. Chronic NOS inhibition prevents adverse lung remodeling and pulmonary arterial hypertension in caveolin-1 knockout mice. *Pulm Pharmacol Ther.* 2008;21(3):507-515.
12. Murata T, Yamawaki H, Hori M, Sato K, Ozaki H, Karaki H. Hypoxia impairs endotheliumdependent relaxation in organ cultured pulmonary artery. *Eur J Pharmacol.* 2001;421(1):45-53.
13. Ou J, Fontana JT, Ou Z, et al. Heat shock protein 90 and tyrosine kinase regulate eNOS NO* generation but not NO* bioactivity. *Am J Physiol Heart Circ Physiol.* 2004;286(2):H561-H569.
14. Konduri GG, Bakhutashvili I, Eis A, Pritchard K Jr. Oxidant stress from uncoupled nitric oxide synthase impairs vasodilation in fetal lambs with persistent pulmonary hypertension. *Am J Physiol Heart Circ Physiol.* 2007;292(4):H1812-H1820.
15. Konduri GG, Ou J, Shi Y, Pritchard KA Jr. Decreased association of HSP90 impairs endothelial nitric oxide synthase in fetal lambs with persistent pulmonary hypertension. *Am J Physiol Heart Circ Physiol.* 2003;285(1):H204-H211.
16. Mahmoud M, Borthwick GM, Hislop AA, Arthur HM. Endoglin and activin receptor-like-kinase 1 are co-expressed in the distal vessels of the lung: implications for two familial vascular dysplasias, HHT and PAH. *Lab Invest.* 2009;89(1):15-25.
17. Toporsian M, Gros R, Kabir MG, et al. A role for endoglin in coupling eNOS activity and regulating vascular tone revealed in hereditary hemorrhagic telangiectasia. *Circ Res.* 2005;96(6):684-692.
18. Toporsian M, Jerkic M, Zhou YQ, et al. Spontaneousadult-onset pulmonary arterial hypertension attributable to increased endothelial oxidative stress in a murine model of hereditary hemorrhagic telangiectasia. *Arterioscler Thromb Vasc Biol.* 2010; 30(3):509-517.
19. Belik J, Jerkic M, McIntyre BA, et al. Agedependent endothelial nitric oxide synthase uncoupling in pulmonary arteries of endoglin heterozygous mice. *Am J Physiol Lung Cell Mol Physiol.* 2009;297(6):L1170-L1178.
20. Jerkic M, Kabir MG, Davies A, et al. Pulmonary hypertension in adult Alk1 heterozygous mice due to oxidative stress. *Cardiovasc Res.* 2011;92(3): 375-384.
21. Trembath RC, Thomson JR, Machado RD, et al. Clinical and molecular genetic features of pulmonary hypertension in patients with hereditary hemorrhagic telangiectasia. *N Engl J Med.* 2001; 345(5):325-334.
22. Harrison RE, Berger R, Haworth SG, et al. Transforming growth factor-beta receptor mutations and pulmonary arterial hypertension in childhood. *Circulation.* 2005;111(4):435-441.
23. Mache CJ, Gamillscheg A, Popper HH, Haworth SG. Early-life pulmonary arterial hypertension with subsequent development of diffuse pulmonary arteriovenous malformations in hereditary haemorrhagic telangiectasia type 1. *Thorax.* 2008;63(1): 85-86.

Key Words—arteriovenous malformations, endoglin, endothelial dysfunction, haploinsufficiency, hereditary hemorrhagic telangiectasia

Correspondence: mtoporsi@bidmc.harvard.edu

Comments

Related Resources

- Repurposing FK506 to Increase BMPR2 Signaling and Improve Pulmonary Arterial Hypertension: A Fast Track From Cells to People
- BMPR2 Silencing Activates ERK1/2-AP1 Signaling Through Upstream Effects of RAF
- Acute Vasoreactivity and Genetic Polymorphisms in IPAH/FPAH Children and Adults
- Vasoreactivity Tests and TGF-B type II Receptor Gene Mutations
- Long-term follow-up and survival of BMPR2 mutation positive vs. negative patients

Nimi Tarango, RNB, MSN, GNP, BC

PH Professional Network Member

Nurse Practitioner
Associate Clinical Professor of Nursing
UCSF Medical Center
San Francisco, California

801 Roeder Road, Ste. 1000, Silver Spring, MD 20910
301-565-3004 | PHAOnlineUniv@PHAssociation.org