Cell Metabolism
Previews

Metabolic Dysfunction in the Pathogenesis of Pulmonary Hypertension

Lewis J. Rubin[1,*]
[1]University of California, San Diego, La Jolla, CA 92093, USA
*Correspondence: ljrubin@ucsd.edu
DOI 10.1016/j.cmet.2010.09.006

Pulmonary artery hypertension is characterized by proliferation in the resistance vessels. A recent study in *Science Translational Medicine* (Sutendra et al., 2010) found that increased fatty acid oxidation and a shift in the glycolysis/glucose oxidation ratio may be central to the pathogenesis of this process, suggesting that these abnormalities comprise novel treatment targets.

Pulmonary hypertension, characterized by a mean pulmonary artery pressure >25 mmHg, is a hemodynamic abnormality shared by a variety of cardiac and pulmonary diseases, including left ventricular dysfunction and valvular disease, chronic obstructive and restrictive lung diseases, and chronic thromboembolic disease. The term pulmonary artery hypertension (PAH) refers to conditions in which intrinsic abnormalities of the resistance pulmonary arteries lead to progressive vascular proliferation and extensive remodeling, ultimately leading to severely elevated pulmonary vascular resistance, right ventricular failure, and death (Chin and Rubin, 2008). PAH is an increasingly frequent cause of death in systemic sclerosis, HIV infection, and congenital heart disease. When PAH occurs in the absence of underlying etiology, it is called idiopathic PAH (IPAH), a rare condition with an annual incidence of 1–2 per million. A familial form of PAH exists that accounts for approximately 20% of cases of "idiopathic" PAH. A number of genetic abnormalities have been identified in this population, notably mutation in the bone morphogenetic protein receptor 2 (BMPR2), a member of the TGF-β superfamily (Morrell, 2010).

The pathogenesis of PAH remains poorly understood. Although a variety of functional abnormalities have been identified, particularly in IPAH, it is unclear whether the process is initiated in the endothelial or smooth muscle cells (Yuan and Rubin, 2005). Nevertheless, the demonstration of endothelial cell dysfunction, including enhanced endothelin synthesis and impaired production of prostacyclin and nitric oxide, has led to the development of targeted therapies, including endothelin receptor antagonists, prostacyclin analogs, and drugs that augment nitric oxide-mediated local effects such as phosphodiesterase type 5 (PDE5) inhibitors (Chin and Rubin, 2008). While these therapies have improved outcomes for patients with PAH, they are not universally effective, nor are they curative, underscoring the need for additional therapies that target upstream pathogenic processes.

It has been known for nearly 70 years that hypoxia results in pulmonary vasoconstriction. In the setting of chronic hypoxia, i.e., in patients with chronic lung disease, this vasoconstriction progresses to vascular remodeling and contributes to chronic pulmonary hypertension. Hypoxic vasoconstriction is unique and intrinsic to pulmonary vascular smooth muscle cells and is due to hypoxia-induced inhibition of the voltage-gated $Kv_{1.5}$ channel, leading to cell membrane depolarization and an influx of calcium into the cytoplasm (Yuan et al., 1993). However, the intracellular link between acute constriction and subsequent cellular proliferation has not been elucidated. The smooth muscle cell as the site of disease initiation in IPAH has also been a source of interest since the suggestion by the eminent British cardiologist Paul Wood over 50 years ago that this disease was associated with a "vasoconstrictive factor." Dysfunctional $Kv_{1.5}$ channels and increased intracellular calcium levels have also been demonstrated in pulmonary artery smooth muscle cells from patients with IPAH, lending support to the notion that intrinsic abnormalities in these cells are also important in the pathogenesis of this disease (Yuan et al., 1998; Remillard et al., 2007; Yu et al., 2004).

A unique feature of PAH cells is their resistance to apoptosis (Krick et al., 2001). This finding, coupled with others that are shared by malignant cells, has led to the "cancer hypothesis" in PAH, i.e., that the growth and proliferation of the pulmonary vasculature is akin to that observed in malignancies (Rai et al., 2008). Despite encouraging results in PAH animal models using anticancer drugs such as the tyrosine kinase inhibitor Imatinib, early clinical trials in PAH have been mixed, in part due to the systemic toxicities of these agents.

In a recent study, Sutendra et al. (2010) hypothesized that PAH may share metabolic abnormalities with cancer that account for the resistance to apoptosis. Specifically, the authors hypothesized that an increase in the rate of glycolysis and impaired glucose oxidation leads to resistance to apoptosis in PAH. In a series of extensive and elegant experiments using animal models of acute and chronic pulmonary hypertension, they found that mice deficient in malonyl-CoA decarboxylase (MCD), a key regulatory enzyme for fatty acid oxidation that helps control the ratio of glucose oxidation and glycolysis, demonstrated attenuated vasoconstriction and vascular remodeling. Additionally, they demonstrated that treatment with metabolic modulators dichloroacetate and trimetazidine, which mimic MCD deletion and decrease the ratio of glycolysis/glucose oxidation, reversed the hemodynamic and vascular proliferation in chronically hypoxic mice and rats with monocrotaline-induced pulmonary hypertension. Linking these observations with ion channel function, they showed that MCD-deficient mice manifested attenuated inhibition of Kv channel activity and decreased cytosolic calcium with hypoxia; furthermore, metabolic inhibitors reduced the elevated

intracellular calcium levels in cells from a patient with IPAH obtained at the time of lung transplantation. Taken together, these findings provide a link between an intrinsic metabolic abnormality of pulmonary vascular cellular mitochondria, affecting acute vasoconstriction and resistance to apoptosis, and vascular remodeling.

While the studies by Sutendra et al. provide important connections between a variety of independent observations and lead to a plausible mechanism of upstream pathogenesis of PAH, there are a number of unanswered questions:

1. The degree of vasculopathy seen in chronic hypoxia is quite modest compared to that observed in PAH, and the former is generally reversible upon restoration of normoxic conditions, while the latter is, at least for now, irreversible. Accordingly, the extrapolation from hypoxic pulmonary hypertension to PAH is tenuous.
2. The translation of findings in animal models of PAH, particularly monocrotaline-induced PAH, to the clinical arena has been disappointing, with a number of drugs or other interventions demonstrating dramatic results in animals and either no effect or, at best, a modest effect in patients.
3. The role of the endothelial cell in the pathogenesis of PAH remains unclear, and these experiments did not include studies of these cells. Thus, it remains unclear whether endothelial dysfunction is an early or late event in the pathogenesis of PAH or whether an endothelial-smooth muscle interaction early in the disease process is important.
4. The impact on proliferation of human cells exposed to the metabolic inhibitors was not investigated, an observation that would have provided a much stronger link between altering intracellular calcium and remodeling.
5. The authors examined cells from a single patient with "IPAH." Whether their observations will be reinforced with experiments from cells obtained from other patients with this or other forms of PAH is unclear.

Despite these limitations, Sutendra et al. have advanced our understanding of the pathogenesis of pulmonary vascular disease and have pointed us in the direction of a new and selective target for therapy. While more work needs to be done before a formal clinical trial of metabolic inhibitors should be entertained, the prospect of reversing the vasculopathy of PAH is exciting and brings a new set of colleagues—experts in metabolism—into the battle.

REFERENCES

Chin, K.M., and Rubin, L.J. (2008). J. Am. Coll. Cardiol. *51*, 1527–1538.

Krick, S., Platoshyn, O., McDaniel, S.S., Rubin, L.J., and Yuan, J.X. (2001). Am. J. Physiol. Lung Cell. Mol. Physiol. *281*, L887–L894.

Morrell, N.W. (2010). Adv. Exp. Med. Biol. *661*, 251–264.

Rai, P.R., Cool, C.D., King, J.A., Stevens, T., Burns, N., Winn, R.A., Kasper, M., and Voelkel, N.F. (2008). Am. J. Respir. Crit. Care Med. *178*, 558–564.

Remillard, C.V., Tigno, D.D., Platoshyn, O., Burg, E.D., Brevnova, E.E., Conger, D., Nicholson, A., Rana, B.K., Channick, R.N., Rubin, L.J., et al. (2007). Am. J. Physiol. Cell Physiol. *292*, C1837–C1853.

Sutendra, G., Bonnet, S., Rochefort, G., Haromy, A., Folmes, K.D., Lopaschuk, G.D., Dyck, J.R., and Michelakis, E.D. (2010). Sci. Transl. Med. *2*, 44ra58.

Yu, Y., Fantozzi, I., Remillard, C.V., Landsberg, J.W., Kunichika, N., Platoshyn, O., Tigno, D.D., Thistlethwaite, P.A., Rubin, L.J., and Yuan, J.X.-J. (2004). Proc. Natl. Acad. Sci. USA *101*, 13861–13866.

Yuan, J.X.J., and Rubin, L.J. (2005). Circulation *111*, 534–538.

Yuan, X.J., Goldman, W.F., Tod, M.L., Rubin, L.J., and Blaustein, M.P. (1993). Am. J. Physiol. *264*, L116–L123.

Yuan, J.X.-J., Aldinger, A.M., Juhaszova, M., Wang, J., Conte, J.V., Jr., Gaine, S.P., Orens, J.B., and Rubin, L.J. (1998). Circulation *98*, 1400–1406.

On Bone-Forming Cells and Blood Vessels in Bone Development

Claire Clarkin[1] and Bjorn R. Olsen[1,*]
[1]Harvard School of Dental Medicine, 188 Longwood Avenue, Boston, MA 02115, USA
*Correspondence: bjorn_olsen@hms.harvard.edu
DOI 10.1016/j.cmet.2010.09.009

Replacement of nonvascular cartilage by bone and bone marrow is a critical step in bone development. In a recent issue of *Developmental Cell*, Maes et al. (2010) report that a distinct population of immature precursors of bone-forming cells migrate into the cartilage in intimate association with invading blood vessels.

The development of most bones, such as bones in the limbs and spine, proceeds via a two-stage process known as endochondral ossification. The architectural modeling of a bone takes place in the location of the future bone via assembly of a template. The template consists of hyaline cartilage, a nonvascular tissue composed of chondrocytes dispersed within a complex extracellular matrix. As the template grows and takes on the shape of the future bone, chondrocytes