

## REVIEW ARTICLE

## MECHANISMS OF DISEASE

## Pulmonary Arterial Hypertension

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**P**ULMONARY HYPERTENSION IS USUALLY CLASSIFIED AS PRIMARY (IDIOPATHIC) or secondary.<sup>1</sup> It is now clear, however, that there are conditions within the category of secondary pulmonary hypertension that resemble primary pulmonary hypertension in their histopathological features and their response to treatment. For this reason, the World Health Organization (WHO) classified pulmonary hypertension into five groups on the basis of mechanisms, rather than associated conditions (Table 1). The most recent revision of the WHO classification uses consistent terminology and defines pulmonary hypertension more precisely than previous versions.<sup>2</sup> Group I of the WHO classification, designated pulmonary arterial hypertension, is the principal focus of this review.

Pulmonary arterial hypertension is defined as a sustained elevation of pulmonary arterial pressure to more than 25 mm Hg at rest or to more than 30 mm Hg with exercise, with a mean pulmonary-capillary wedge pressure and left ventricular end-diastolic pressure of less than 15 mm Hg.<sup>3</sup> Pulmonary arterial hypertension comprises idiopathic pulmonary arterial hypertension (formerly, primary pulmonary hypertension); pulmonary arterial hypertension in the setting of collagen vascular disease (e.g., in localized cutaneous systemic sclerosis, also known as the CREST syndrome [calcinosis cutis, Raynaud's phenomenon, esophageal dysfunction, sclerodactyly, and telangiectasia]), portal hypertension, congenital left-to-right intracardiac shunts, and infection with the human immunodeficiency virus (HIV); and persistent pulmonary hypertension of the newborn. The histologic appearance of lung tissue in each of these conditions is similar: intimal fibrosis, increased medial thickness, pulmonary arteriolar occlusion, and plexiform lesions predominate.<sup>4</sup>

Although the pathogenesis of most forms of pulmonary arterial hypertension is unknown, there have been many recent developments, especially pertaining to the molecular genetics and cell biology of idiopathic pulmonary arterial hypertension. In this review, we discuss these developments and relate them to other forms of pulmonary arterial hypertension, when appropriate. Treatment is discussed briefly as it relates to the disease mechanism; more information on treatment can be found in recent reviews of this topic.<sup>5,6</sup>

## IMBALANCE OF VASCULAR EFFECTORS

The main vascular changes in pulmonary arterial hypertension are vasoconstriction, smooth-muscle cell and endothelial-cell proliferation, and thrombosis. These findings suggest the presence of perturbations in the normal relationships between vasodilators and vasoconstrictors, growth inhibitors and mitogenic factors, and antithrombotic and prothrombotic determinants. These homeostatic imbalances are probably consequences of pulmonary endothelial-cell dysfunction or injury.

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**PROSTACYCLIN AND THROMBOXANE A<sub>2</sub>**

Prostacyclin and thromboxane A<sub>2</sub> are major arachidonic acid metabolites of vascular cells. Prostacyclin, a potent vasodilator, inhibits platelet activation and has antiproliferative properties; in contrast, thromboxane A<sub>2</sub> is a potent vasoconstrictor and platelet agonist.<sup>7</sup> In pulmonary arterial hypertension, the imbalance between these two molecules is shifted toward thromboxane A<sub>2</sub><sup>8</sup>: in the urine of patients with pulmonary hypertension, the levels of a metabolite of prostacyclin (6-keto-prostacyclin F<sub>2α</sub>) are decreased, whereas the levels of a metabolite of thromboxane A<sub>2</sub> (thromboxane B<sub>2</sub>) are increased. Furthermore, the production of prostacyclin synthase is decreased in the small and medium-sized pulmonary arteries of patients with pulmonary hypertension, particularly those with idiopathic pulmonary arterial hypertension.<sup>9</sup>

**ENDOTHELIN-1**

Endothelin-1, a potent vasoconstrictor, stimulates the proliferation of pulmonary-artery smooth-muscle cells.<sup>10,11</sup> The plasma levels of endothelin-1 are increased in pulmonary arterial hypertension,<sup>12-14</sup> and the level of endothelin-1 is inversely proportional to the magnitude of the pulmonary blood flow and cardiac output, suggesting that these hemodynamic changes are influenced directly by this vascular effector.

**NITRIC OXIDE**

The synthesis of nitric oxide, a potent vasodilator and inhibitor of platelet activation and vascular smooth-muscle cell proliferation, is catalyzed by the family of nitric oxide synthase enzymes. Decreased levels of the endothelial isoform of nitric oxide synthase have been observed in the pulmonary vascular tissue of patients with pulmonary hypertension, particularly those with idiopathic pulmonary arterial hypertension.<sup>15,16</sup> Endothelial nitric oxide synthase is, however, increased in the plexiform lesions of idiopathic pulmonary arterial hypertension, where it probably promotes pulmonary endothelial-cell proliferation.<sup>17</sup>

**SEROTONIN**

Serotonin (5-hydroxytryptamine) is a vasoconstrictor that promotes smooth-muscle cell hypertrophy and hyperplasia.<sup>18</sup> Elevated levels of plasma serotonin and reduced content of serotonin in platelets have been found in idiopathic pulmonary arterial hypertension<sup>19</sup> and persist even after the normalization of pulmonary-artery pressures following lung transplantation. A platelet defect that results in a reduced uptake of serotonin (i.e.,  $\delta$  storage pool disease) has been associated with pulmonary hypertension.<sup>20</sup> Among patients who took the appetite suppressant dexfenfluramine, which increases the release of serotonin from platelets and inhibits its reuptake, for more than three months, the incidence of pulmonary arterial hypertension increased.<sup>21</sup> Recently, mutations in the serotonin transporter (5-HTT), the 5-hydroxytryptamine 2b receptor (5-HT<sub>2B</sub>), or both have been described in platelets and lung tissue from patients with pulmonary arterial hypertension.<sup>22</sup> Nevertheless, the level of serotonin itself is probably not a determinant of pulmonary hypertension, because selective serotonin-reuptake inhibitors (SSRIs), which increase serotonin levels but inhibit serotonin transport, are

**Table 1. The Revised World Health Organization Classification of Pulmonary Hypertension.\***

Group I. Pulmonary arterial hypertension
Idiopathic (primary)
Familial
Related conditions: collagen vascular disease, congenital systemic-to-pulmonary shunts, portal hypertension, HIV infection, drugs and toxins (e.g., anorexigens, rapeseed oil, L-tryptophan, methamphetamine, and cocaine); other conditions: thyroid disorders, glycogen storage disease, Gaucher's disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, myeloproliferative disorders, splenectomy
Associated with significant venous or capillary involvement
Pulmonary veno-occlusive disease
Pulmonary-capillary hemangiomatosis
Persistent pulmonary hypertension of the newborn
Group II. Pulmonary venous hypertension
Left-sided atrial or ventricular heart disease
Left-sided valvular heart disease
Group III. Pulmonary hypertension associated with hypoxemia
Chronic obstructive pulmonary disease
Interstitial lung disease
Sleep-disordered breathing
Alveolar hypoventilation disorders
Chronic exposure to high altitude
Developmental abnormalities
Group IV. Pulmonary hypertension due to chronic thrombotic disease, embolic disease, or both
Thromboembolic obstruction of proximal pulmonary arteries
Thromboembolic obstruction of distal pulmonary arteries
Pulmonary embolism (tumor, parasites, foreign material)
Group V. Miscellaneous
Sarcoidosis, pulmonary Langerhans'-cell histiocytosis, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)

\* The table has been adapted from Simonneau et al.<sup>2</sup>

not associated with an increased incidence of pulmonary hypertension and may, in fact, be protective in the setting of hypoxia.<sup>23</sup>

#### ADRENOMEDULLIN

Adrenomedullin dilates pulmonary vessels, increases the pulmonary blood flow, and is synthesized by several cell populations in the normal lung. High levels of messenger RNA (mRNA) for adrenomedullin and its receptor in the lung suggest a homeostatic role for this peptide in the pulmonary circulation.<sup>24</sup> The plasma levels of adrenomedullin are elevated in both pulmonary arterial hypertension and pulmonary hypertension associated with hypoxemia,<sup>25,26</sup> and the elevation correlates with increases in the mean right atrial pressure, pulmonary vascular resistance, and the mean pulmonary arterial pressure.<sup>27</sup> Current data suggest, however, that increased adrenomedullin is a marker of pulmonary hypertension, rather than a cause.

#### VASOACTIVE INTESTINAL PEPTIDE

Vasoactive intestinal peptide, a potent systemic vasodilator, decreases pulmonary-artery pressure and pulmonary vascular resistance in rabbits with monocrotaline-induced pulmonary hypertension<sup>28</sup> and in healthy human subjects<sup>29</sup>; it also inhibits platelet activation<sup>30</sup> and vascular smooth-muscle cell proliferation.<sup>31</sup> A recent study reported decreased levels of vasoactive intestinal peptide in the serum and the lungs in patients with pulmonary arterial hypertension; treatment with inhaled vasoactive intestinal peptide improved the clinical course and the hemodynamics in these patients.<sup>32</sup>

#### VASCULAR ENDOTHELIAL GROWTH FACTOR

In acute and chronic hypoxia, the production of vascular endothelial growth factor (VEGF) is increased and that of its receptors, VEGF receptor-1 (kinase-domain related [KDR], or Flk) and VEGF receptor-2 (Flt), in the lung.<sup>33</sup> In pulmonary arterial hypertension, disordered angiogenic responses appear to underlie the formation of plexiform lesions and the clonal expansion of endothelial cells within the lesions. VEGF mRNA and protein have been detected in such lesions along with increased amounts of VEGF receptor-2, hypoxia-inducible factor  $\alpha$ , and hypoxia-inducible factor  $\beta$  and decreased amounts of three signaling molecules essential for the angiogenic response to VEGF, phosphoinositide-3-kinase, Akt, and src.<sup>34</sup> These

observations suggest an abnormal angiogenic response to hypoxia owing to abnormal signaling responses in pulmonary arterial hypertension.

In summary, there is an imbalance of the vascular effectors in pulmonary arterial hypertension that favors vasoconstriction, vascular-cell proliferation, and thrombosis (Fig. 1). The treatments developed on the basis of these observations (i.e., epoprostenol, nitric oxide, and endothelin-receptor antagonists) have been effective in improving the pulmonary vascular hemodynamics, clinical status, and, in some cases, survival in idiopathic and other forms of pulmonary arterial hypertension. None of these vasoactive molecules, however, have yet been conclusively linked to the primary pathogenesis of the disease.

#### ASSOCIATED ENVIRONMENTAL FACTORS

Among the environmental factors associated with an increased risk of the development of pulmonary arterial hypertension, three — hypoxia, anorexigens, and central nervous system stimulants — have plausible mechanistic underpinnings.

#### HYPOXIA

Hypoxia induces vasodilation in systemic vessels, but it induces vasoconstriction in the pulmonary vasculature. The acute effect of hypoxia is regulated, in part, by two endothelial cell-derived vasoconstrictors, endothelin and serotonin, and, in part, by hypoxia-mediated changes in ion-channel ac-

Vasoconstriction	Cell Proliferation	Thrombosis
Increased TxA <sub>2</sub>	Increased VEGF	Increased TxA <sub>2</sub>
Decreased PGI <sub>2</sub>	Decreased PGI <sub>2</sub>	Decreased PGI <sub>2</sub>
Decreased NO	Decreased NO	Decreased NO
Increased ET-1	Increased ET-1	
Increased 5-HT	Increased 5-HT	Increased 5-HT
Decreased VIP	Decreased VIP	Decreased VIP

**Figure 1. Mediators of Pulmonary Vascular Responses in Pulmonary Arterial Hypertension.**

TxA<sub>2</sub> denotes thromboxane A<sub>2</sub>, PGI<sub>2</sub> prostaglandin I<sub>2</sub> (prostacyclin), NO nitric oxide, ET-1 endothelin-1, 5-HT 5-hydroxytryptamine (serotonin), VEGF vascular endothelial growth factor, and VIP vasoactive intestinal peptide.

tivity in smooth-muscle cells in the pulmonary arteries.<sup>35</sup> Acute hypoxia inhibits the function of voltage-gated potassium channels in these smooth-muscle cells, resulting in membrane depolarization, an increase in the concentration of cytoplasmic calcium, and vasoconstriction.<sup>36</sup> Acute hypoxia causes reversible changes in vascular tone, whereas chronic hypoxia induces structural remodeling, the proliferation and migration of vascular smooth muscle, and an increase in the deposition of vascular matrix. Although hypoxia is not of central importance in the initial development of pulmonary arterial hypertension, it may contribute to the remodeling of the pulmonary vasculature as the disease progresses.

#### **ANOREXIGENS**

An association between the use of anorexigenic agents and the development of pulmonary arterial hypertension was initially observed in the 1960s, when an epidemic of idiopathic pulmonary arterial hypertension was noted in Europe after the introduction of the anorexigen aminorex fumarate.<sup>37</sup> Although this medication was withdrawn from the market, structurally related compounds, such as fenfluramine and dexfenfluramine, were developed subsequently, in the 1980s. The use of these agents has also been associated with an increased risk of pulmonary arterial hypertension.<sup>21</sup> Although the incidence of pulmonary arterial hypertension increases with the duration of use, an elevation in pulmonary pressure can occur after as little as three to four weeks of exposure to these agents.<sup>38,39</sup>

#### **CENTRAL NERVOUS SYSTEM STIMULANTS**

The use of the central nervous system stimulants methamphetamine and cocaine has been associated with an increased risk of pulmonary arterial hypertension.<sup>40</sup> Although it has been suggested that contaminants in synthesized methamphetamine play a causative role,<sup>41</sup> pulmonary hypertension occurs after the use of contaminant-free fenfluramines and aminorex fumarate, both amphetamine-like anorexigenic agents. In an autopsy study of 20 heavy users of cocaine, the lungs of four showed medial hypertrophy of the pulmonary arteries without evidence of foreign-body microembolization — findings consistent with pulmonary arterial hypertension.<sup>42</sup> The cause of these changes is unknown, and whether the stimulants alone can cause pulmonary arterial hypertension is unclear.

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#### **OTHER ASSOCIATED CONDITIONS**

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Several coexisting conditions have been associated with pulmonary arterial hypertension. Those with plausible mechanistic links include scleroderma, infection with the human immunodeficiency virus (HIV), human herpesvirus (HHV), portal hypertension, thrombocytosis, hemoglobinopathies, and hereditary hemorrhagic telangiectasia.

#### **SCLERODERMA**

A pulmonary arteriopathy occurs in limited systemic sclerosis (i.e., tight skin limited to the fingers, with digital ulcers and often pulmonary fibrosis), especially in the CREST variant.<sup>43-45</sup> At autopsy, up to 80 percent of patients with the CREST syndrome have histopathological changes consistent with pulmonary arterial hypertension; however, in life, only 10 to 15 percent have clinically significant pulmonary hypertension. Histologic features consistent with pulmonary arterial hypertension and clinically evident pulmonary hypertension have occasionally been observed in systemic lupus erythematosus, mixed connective-tissue disease, and rheumatoid arthritis. In each case, there was an association between the occurrence of pulmonary arterial hypertension and Raynaud's phenomenon, suggesting similarities in the pathogenesis of these vasculopathies.<sup>46</sup>

#### **INFECTION WITH HIV**

An association between HIV infection and pulmonary arterial hypertension was first reported in 1991; the initial cases occurred primarily in patients with hemophilia, who acquired HIV infection after receiving factor VIII-enriched plasma.<sup>47,48</sup> Since then, the number of cases has increased and now includes people who acquired HIV infection by any route. In population studies in which echocardiography was used to estimate pulmonary-artery pressure, the incidence of pulmonary hypertension was approximately 0.5 percent among patients with HIV infection, a rate 6 to 12 times as high as in the general population. The occurrence of pulmonary arterial hypertension is independent of the CD4 cell count, but it appears to be related to the duration of HIV infection. Many of these patients also have foreign-body emboli as a result of the use of intravenous drugs or portal hypertension due to a concomitant infection with hepatitis B or C. Both these disease entities have been associated with pulmo-

nary hypertension. Because HIV does not directly infect endothelial cells, the mechanism of pulmonary hypertension in HIV infection is unclear.

#### HUMAN HERPESVIRUS

Human herpesvirus 8 (HHV-8) is the causative agent of Kaposi's sarcoma.<sup>49</sup> On the basis of the histologic similarities between the plexiform lesions in pulmonary arterial hypertension and endothelial abnormalities in Kaposi's sarcoma, a recent study examined markers of HHV-8 infection in pulmonary arterial hypertension<sup>50</sup> and found evidence of HHV-8 infection in specimens of lung tissue obtained from 10 of 16 patients with pulmonary arterial hypertension.

#### PORTAL HYPERTENSION

There is an uncommon association between portal hypertension and pulmonary arterial hypertension. In a large autopsy series, histologic changes consistent with pulmonary arterial hypertension were found in 0.73 percent of patients with cirrhosis, which is six times the prevalence found on autopsy in persons without portal hypertension.<sup>51</sup> Hemodynamic studies have found pulmonary hypertension in 2 to 5 percent of patients with cirrhosis<sup>52</sup>; the prevalence may be higher (3.5 to 8.5 percent) in patients referred for liver transplantation.<sup>53</sup> Right heart catheterization disclosed the presence of pulmonary hypertension in approximately 6 percent of patients undergoing evaluation for liver transplantation.<sup>54</sup> The diagnosis of pulmonary hypertension is usually made within four to seven years after the diagnosis of portal hypertension<sup>55</sup> but, rarely, may precede it.<sup>56</sup> In addition, the risk of pulmonary arterial hypertension increases with the duration of portal hypertension.<sup>56</sup> The mechanism of this association is unclear, but cirrhosis without portal hypertension appears to be insufficient for the development of pulmonary arterial hypertension.

#### THROMBOCYTOSIS

Pulmonary arterial hypertension has been reported in patients with chronic myelodysplastic syndromes with thrombocytosis.<sup>57,58</sup> Of 26 patients with a chronic myelodysplastic syndrome and unexplained pulmonary hypertension, 14 had elevated platelet counts (median, approximately 600,000 per cubic millimeter).<sup>58</sup> The association between pulmonary arterial hypertension and the myelo-

dysplastic syndromes is probably caused by several different features of this syndrome, including splenectomy, portal hypertension, pulmonary vascular obstructive disease as a result of chemotherapy, and the infiltration of hematopoietic cells into the pulmonary parenchyma.<sup>58</sup> However, a correlation between the platelet count and the level of pulmonary hypertension has been found, and in two cases, there was evidence of pulmonary-artery obstruction by megakaryocytes, suggesting that platelets and their precursors play a direct role in pathogenesis.<sup>59</sup> In addition, rare cases of pulmonary hypertension have been reported in patients with idiopathic thrombocytopenia.<sup>60,61</sup> It is possible that platelet-derived serotonin, platelet-derived growth factor, or transforming growth factor  $\beta$  (TGF- $\beta$ ) are important in the development of pulmonary arterial hypertension in such patients. These agents derive from platelets and are potent stimuli of smooth-muscle cell proliferation; in an animal model of pulmonary vascular injury, normalization of the platelet count retarded the development of pulmonary arterial hypertension.<sup>62</sup>

#### HEMOGLOBINOPATHIES

Several studies have documented pulmonary hypertension and right ventricular dysfunction in patients with thalassemia, particularly homozygous  $\beta$ -thalassemia.<sup>63,64</sup> Although one study reported evidence of pulmonary hypertension in 75 percent of patients with  $\beta$ -thalassemia, this study and others relied on echocardiography for the diagnosis of pulmonary hypertension and therefore probably overestimated its incidence.

In sickle cell anemia, the estimated incidence of pulmonary hypertension, as determined on echocardiography, varies from 8 percent to 30 percent.<sup>65</sup> In a recent study of 34 adults with sickle cell disease who underwent catheterization,<sup>66</sup> 20 received a diagnosis of pulmonary hypertension, and several of these adults had elevated pulmonary-capillary wedge pressures consistent with left ventricular diastolic dysfunction. The mean pulmonary-artery pressure was inversely related to survival: each increase of 10 mm Hg in the mean pulmonary-artery pressure was associated with an increase by a factor of 1.7 in the risk of death. Very recent data confirm that pulmonary hypertension increases the risk of death in patients with sickle cell disease.<sup>67</sup> Historically, recurrent episodes of acute chest syndrome were considered to be the most important

risk factor for the development of pulmonary arterial hypertension<sup>68</sup>; however, recent data suggest this may not be the case.

The destruction of bioactive nitric oxide by free hemoglobin<sup>69</sup> and an increase in the production of reactive oxygen species<sup>70,71</sup> may be more important in the development of pulmonary hypertension in patients with a hemolytic anemia than in those without a hemolytic anemia. For example, in sickle cell anemia, the plasma levels of oxyhemoglobin are high owing to intravascular hemolysis; this cell-free hemoglobin can impair responses to intrinsic and exogenously delivered nitric oxide. In patients with sickle cell anemia, there are also increased circulating and intracellular levels of reactive oxygen species, which can inactivate nitric oxide.

#### HEREDITARY HEMORRHAGIC TELANGIECTASIA

Pulmonary hypertension that is clinically and histologically indistinguishable from idiopathic pulmonary arterial hypertension occurs in approximately 15 percent of cases of hereditary hemorrhagic telangiectasia (the Osler–Rendu–Weber syndrome), an autosomal dominant vascular dysplasia.<sup>72,73</sup> Mutations in two genes encoding the TGF- $\beta$  receptors, endoglin and activin-receptor–like kinase 1 (ALK1), have been associated with the pulmonary hypertension of hereditary hemorrhagic telangiectasia.

#### ASSOCIATED GENETIC ABNORMALITIES

Approximately 100 families worldwide have been identified as having idiopathic pulmonary arterial hypertension.<sup>74–76</sup> The familial form accounts for at least 6 percent of all cases of pulmonary arterial hypertension, and its distribution between female and male patients, the age at onset, and its natural history are similar to those in the sporadic form. Segregation analysis of affected pedigrees shows an autosomal dominant inheritance, but only 10 to 20 percent of the carriers of the relevant mutation have evidence of pulmonary arterial hypertension. Inheritance of the appropriate genetic mutation shows genetic anticipation: in each successive generation in which the disease develops, it occurs at a younger age and with greater severity than in the preceding generation.

#### TGF- $\beta$ RECEPTOR PATHWAY

Two genes in the ubiquitous TGF- $\beta$  receptor family have been strongly linked to familial pulmo-

nary arterial hypertension.<sup>74</sup> The first gene, bone morphogenetic protein receptor type 2 (BMPR2), modulates the growth of vascular cells by activating the intracellular pathways of Smad and LIM (Lin-11, Isl-1, and Mec-3 protein) kinase.<sup>77</sup> Under normal conditions, bone morphogenetic proteins 2, 4, and 7 signal through heterodimeric complexes of BMPR2 and type 1 receptors to suppress the growth of vascular smooth-muscle cells. More than 45 different mutations in BMPR2 have been identified in patients with familial pulmonary arterial hypertension.<sup>75,76</sup> Functional studies have shown that point mutations and truncations in the kinase domain exert dominant negative effects on receptor function.<sup>78</sup> Because of incomplete penetrance and genetic anticipation (i.e., an increased familial prevalence of the phenotype in successive generations), it is probable that the BMPR2 mutations are necessary, but insufficient alone, to account for the clinical expression of the disease.

A rare group of patients with hereditary hemorrhagic telangiectasia and idiopathic pulmonary arterial hypertension was found to harbor mutations in another member of the TGF- $\beta$  receptor family, ALK1.<sup>75</sup> As with BMPR2 mutations, mutations in this type 1 receptor are believed to result in growth-promoting Smad-dependent signaling.

Perhaps as many as 10 to 26 percent of patients with sporadic idiopathic pulmonary arterial hypertension also bear a mutation of a member of the TGF- $\beta$  receptor family.<sup>79</sup> Recently, Du and colleagues<sup>80</sup> have argued that all forms of pulmonary arterial hypertension also have defects in a common vascular signaling pathway that involves angiotensin-1 and the phosphorylated form of its endothelial-specific receptor, TIE2. These investigators showed that this signaling pathway is up-regulated in the lungs of patients with pulmonary hypertension, regardless of the cause of the disease; the increase in angiotensin signaling is accompanied by a decrease in another member of the TGF- $\beta$  receptor family, BMPR1A, a complementary type 1 receptor required for normal BMPR2 signaling. Some of these observations, however, run counter to previous findings regarding the role of angiotensin in the pulmonary vasculature.<sup>81,82</sup>

#### SEROTONINERGIC PATHWAY

The increased serotonin-dependent proliferation of cultured pulmonary vascular smooth-muscle cells in specimens obtained from patients with idiopathic pulmonary arterial hypertension is, in part, a consequence of an increase in the serotonin trans-

porter 5-HTT.<sup>22</sup> The L-allelic variant of the 5HTT gene is associated with an increased expression of the transporter and an increase in the growth of vascular smooth-muscle cells, and it is more prevalent among patients with idiopathic pulmonary arterial hypertension than among controls.

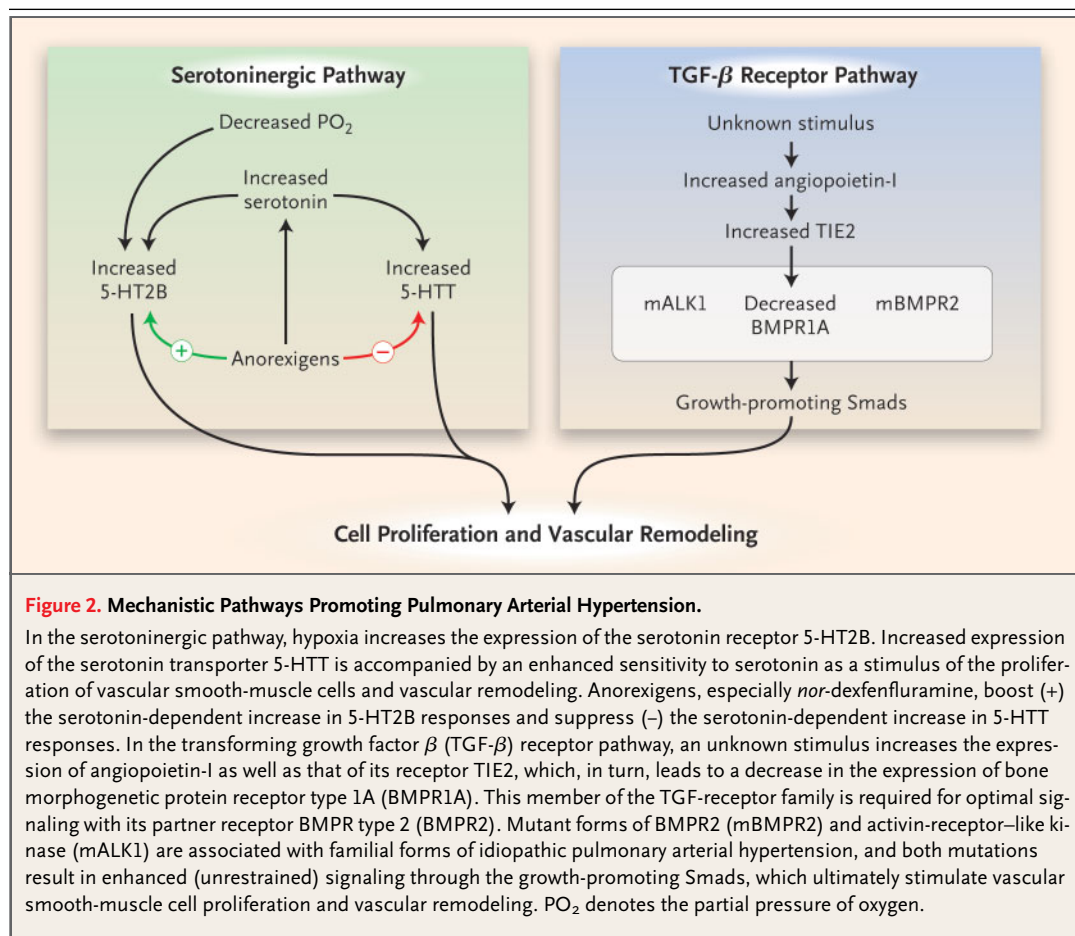
A complementary study by Launay and colleagues<sup>83</sup> showed that hypoxia-induced pulmonary arterial hypertension in mice is associated with an increase in the expression of 5-HT2B, resulting in serotonin-dependent vascular remodeling. In addition, they showed that the main metabolite of dexfenfluramine, *nor*-dexfenfluramine, is a potent vascular-cell growth-promoting agonist for this receptor, thus linking anorexigenic pulmonary arterial hypertension to signaling pathways in pulmonary vascular cells that are up-regulated by hypoxia and activated by serotonin.

Possible associations among these genetically determined pathways are summarized in Figure 2. Environmental factors that may influence the func-

tioning of the pathways are also included in the figure.

#### MOLECULAR BASIS OF TREATMENT STRATEGIES

There is no cure for pulmonary arterial hypertension. Treatment, however, has improved dramatically during the past decade, offering both relief from symptoms and prolonged survival. The mainstays of current medical therapy fall into several classes, including vasodilators, anticoagulants, antiplatelet agents, antiinflammatory therapies, and vascular-remodeling therapies. Many of the most effective agents have pleiotropic effects. For example, epoprostenol is a vasodilator, a platelet inhibitor, and an antiinflammatory agent, whereas the endothelin-receptor antagonist bosentan is a vasodilator, an antiinflammatory agent, and a remodeling mediator. Many of these therapies can be viewed as pharmacologic surrogates for endothe-



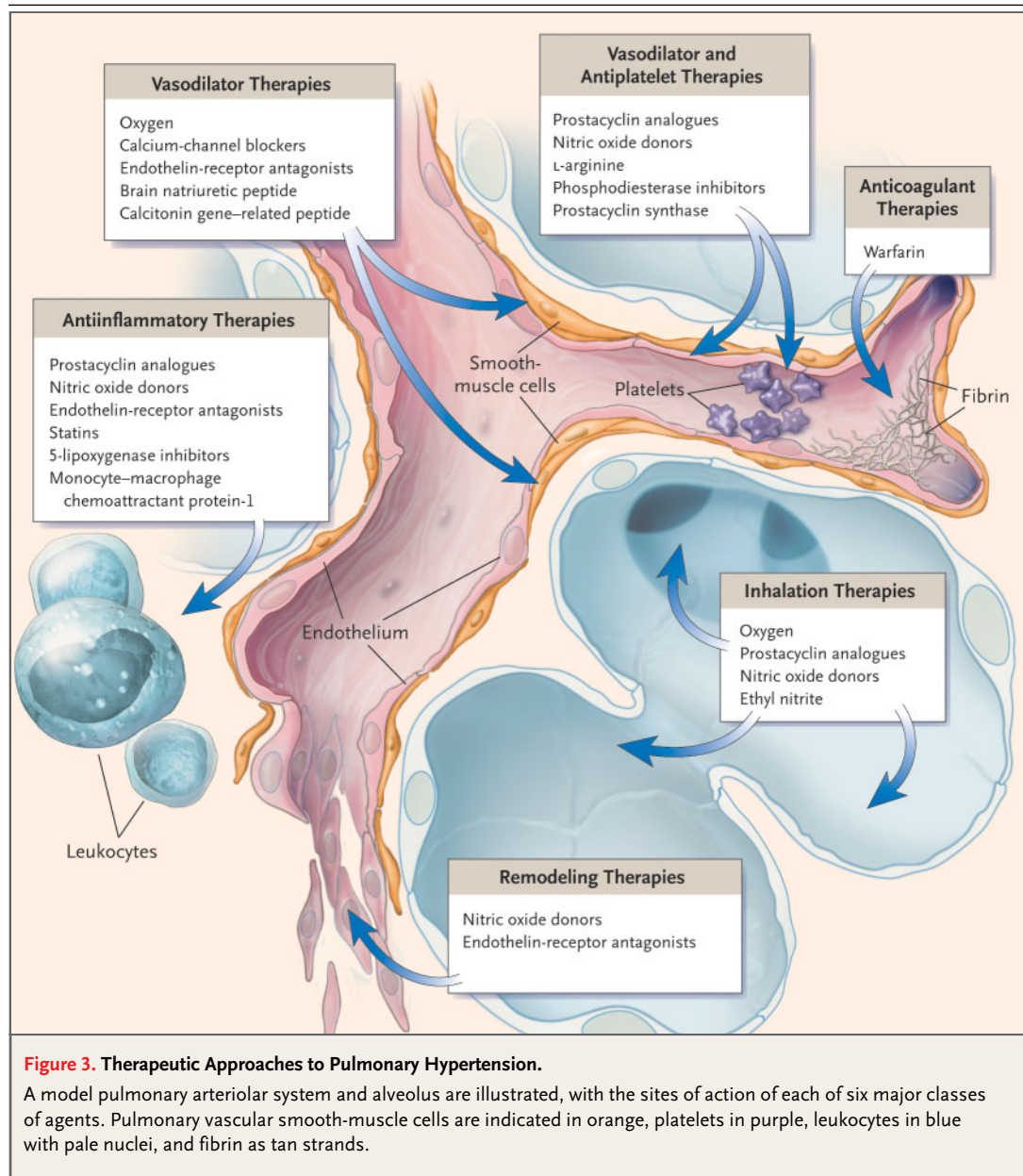
lial effectors and as strategies for restoring pulmonary vascular homeostasis. Owing to limitations of space, these therapies are not reviewed here, but their sites of action are illustrated in Figure 3.

CONCLUSIONS

Pulmonary arterial hypertension comprises a group of clinical and pathophysiological entities with similar features but a variety of underlying causes. Because the range of medical conditions and envi-

ronmental exposures associated with pulmonary arterial hypertension is wide, it is difficult to envision a unifying pathogenic mechanism. Although there probably are genetic determinants, environmental exposures, and acquired disorders that predispose patients to pulmonary arterial hypertension, it is clear that none of the factors described in this review are sufficient alone to activate the pathways essential to the development of this vascular disease.

It is also likely that clinically apparent pulmo-

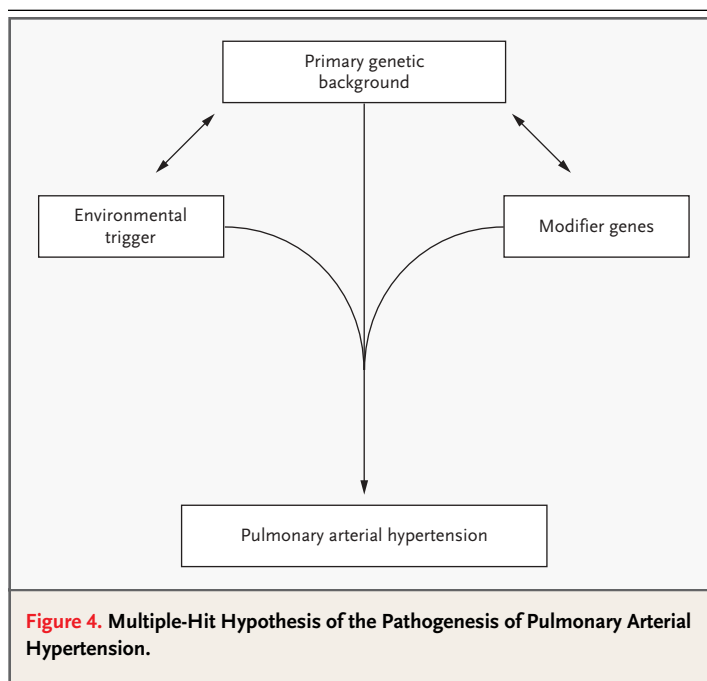




nary arterial hypertension is an end-stage phenotype that represents a final common manifestation of multiple preclinical, intermediate phenotypes. For example, some cases of pulmonary arterial hypertension are likely to be a consequence of an initial pathogenic event that involves the pulmonary vascular smooth-muscle cell (e.g., familial idiopathic pulmonary arterial hypertension with *BMPR2* mutations), whereas other cases are likely to be a consequence of an initial pathogenic event that involves the pulmonary endothelial cell (e.g., familial idiopathic pulmonary arterial hypertension in hereditary hemorrhagic telangiectasia). Thus, an understanding of the preclinical disease in at-risk populations will be critical for identifying the primary pathogenic mechanisms.

Because clinically apparent disease occurs in only a small percentage of the carriers of the *BMPR2*, *ALK1*, and *5HTT* mutations, it is probable that there are modifier genes, modifying environmental triggers, or both, and that these genes and environmental factors are important in the pathogenesis of the disease (Fig. 4). Thus, a multiple-hit theory has been suggested, similar to that often invoked for the development of cancers in which a susceptible person with a genetic predisposition (i.e., in the form of polymorphisms or mutations) requires additional insults before the disease is manifested.

If there were a unifying molecular mechanism involved in the development of pulmonary arterial hypertension, it might involve TGF- $\beta$  signaling. Because the TGF- $\beta$  receptors are important in cell proliferation and apoptosis, a decrease in bone morphogenetic protein or in its associated signaling pathways could result in a loss of the antiproliferative or apoptotic mechanisms in the pulmo-



**Figure 4. Multiple-Hit Hypothesis of the Pathogenesis of Pulmonary Arterial Hypertension.**

nary vasculature and thereby promote the vascular changes observed in patients with pulmonary arterial hypertension. Expanded natural-history studies and further evaluation of persons at risk for pulmonary arterial hypertension (e.g., those with mutations of the TGF- $\beta$  pathway and other identified mutations), as well as a better understanding of the disease-modifying genetic and acquired determinants, will provide improved insight into the relation between these genotypes and this complicated phenotype.

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