Deficiency of Urokinase-Type Plasminogen Activator–Mediated Plasmin Generation Impairs Vascular Remodeling During Hypoxia-Induced Pulmonary Hypertension in Mice

Marcel Levi, MD, PhD; Lieve Moons, PhD; Ann Bouché; Steve D. Shapiro, MD;Desiré Collen, MD, PhD; Peter Carmeliet, MD, PhD

Background—Chronic hypoxia results in the development of pulmonary hypertension and subsequent right heart failure. A role of the plasminogen system in the pathogenesis of pulmonary hypertension and pulmonary vascular remodeling has been suggested.

Methods and Results—Mice with targeted deficiency of the gene encoding tissue-type plasminogen activator (t-PA−/−), urokinase-type plasminogen activator (u-PA−/−), u-PA receptor (u-PAR−/−), or plasminogen (plg−/−) were subjected to hypoxic conditions. Hypoxia caused a significant 2.5-fold rise in right ventricular pressure in wild-type mice. Deficiency of u-PA or plasminogen prevented this increase in right ventricular pressure, t-PA−/− mice showed changes that were fully comparable with wild-type mice, and u-PAR−/− mice showed a partial response. Hypoxia induced an increase in smooth muscle cells within pulmonary arterial walls and a vascular rarefaction in the lungs of wild-type but not of u-PA−/− or plg−/− mice. Elastic lamina fragmentation, observed in hypoxic wild-type but not in u-PA or plasminogen-deficient mice, suggested that proliferation of vascular smooth muscle cells was dependent on u-PA–mediated elastic membrane degradation. Hypoxia-induced right ventricular remodeling in wild-type mice, characterized by cardiomyocyte hypertrophy and increased collagen contents, was not seen in u-PA−/− and plg−/− mice.

Conclusions—Loss of the u-PA or plasminogen gene protects against the development of hypoxia-induced pulmonary hypertension and pulmonary vascular remodeling. These observations point to an essential role of u-PA–mediated plasmin generation in the adaptive response to chronic hypoxia and the occurrence of hypoxic pulmonary vascular disease. (Circulation. 2001;103:2014-2020.)

Key Words plasminogen ■ plasminogen activators ■ pulmonary heart disease ■ vasculature ■ remodeling

Hypoxia is one of the most potent stimuli for the formation of new blood vessels (angiogenesis), and it mediates vasodilation of vessels, thereby improving tissue perfusion.1 Lung vessels, however, react to acute hypoxia with constriction rather than dilation, in part through upregulation of vasoactive substances.2–4 Furthermore, hypoxia causes pulmonary vascular cells to proliferate in contrast to the usual growth-suppressive effect of hypoxia on many other cell types.2–6 On prolonged hypoxia, pulmonary vessels undergo significant structural changes involving medial thickening of arteries caused by smooth muscle cell accumulation and matrix deposition and extension of a muscular wall in intra-acinar vessels.7 The latter may result from increased proliferation of smooth muscle cells to more distal uncovered vessels or from recruitment and differentiation of pulmonary fibroblasts or pericytes to contractile smooth muscle cells. Another characteristic feature of vascular remodeling during pulmonary hypertension involves rarefaction of pulmonary arteries.8 Although poorly understood, rarefaction presumably reflects an adaptive structural response to prune insufficiently perfused “ghost” arterioles formed after severe microvascular constriction.9 As a consequence, pulmonary hypertension and right ventricular hypertrophy may develop, ultimately progressing to right heart failure. This constitutes a major cause of cardiopulmonary morbidity and mortality, for example, in patients with chronic obstructive lung disease, for which few medical treatments exist.

The precise molecular mechanisms that play a role in the pathogenesis of pulmonary hypertension and the structural changes in the pulmonary vasculature are only partly

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Pulmonary vasconstriction appears to be of importance, and both endothelin and angiotensin have been implicated as important mediators. In contrast, the observation that mice deficient in endothelial nitric oxide synthase (eNOS) were found to develop excessive pulmonary hypertension, whereas adenoviral NOS gene transfer prevented hypoxia-induced pulmonary hypertension point to an important role of NO in the prevention of hypoxia-induced pulmonary vasconstriction. In addition, several vascular cell mitogens such as heparin-binding epidermal growth factor, vascular endothelial cell growth factor, and platelet-derived growth factor appear to be implicated in the pathogenesis of pulmonary hypertension. Last, activation of proteases, in particular elastase, may be essential for extracellular matrix degradation associated with pulmonary vascular remodeling. Elastase was also shown to be able to induce the release of growth factors (such as basic fibroblast growth factor [b-FGF]) from the extracellular matrix, which may further contribute to pulmonary artery smooth muscle proliferation.

Several observations point to an additional role of the plasminogen system in pulmonary hypertension. Similar to the role of elastase in extracellular matrix remodeling, there is evidence suggesting that enhanced plasmin proteolysis may contribute to pulmonary vascular remodeling. Indeed, hypoxia increases expression of u-PAR (the cellular receptor of urokinase-type plasminogen activator [u-PA]), enhances plasma fibrinolytic activity, and upregulates expression of plasminogen (plg) activators during ventricular hypertrophy in response to hypoxia or overloading. Interestingly, and also similar to elastase, plasmin has been shown to induce the release of b-FGF from the extracellular matrix.

To further investigate the role of the plasminogen system in the pathogenesis of pulmonary hypertension and right ventricular remodeling, mice with specific deficiencies in plasminogen, tissue-type plasminogen activator (t-PA), u-PA, or u-PAR were subjected to hypoxic conditions. The present findings implicate an important role of u-PA–mediated plasmin proteolysis in hypoxia-induced pulmonary vascular remodeling and subsequent right ventricular hypertrophy, which potentially might have important consequences for future therapeutic strategies in patients with (evolving) pulmonary hypertension.

**Methods**

**Animals and Experimental Protocol**

The experiments were approved by the institutional review board and were conducted according to the guidelines for animal experiments of the National Institutes of Health. Transgenic mice and appropriate wild-type control mice were studied after being exposed to chronic hypoxia, as compared with normoxic conditions (controls). Experimental groups (n = 11 to 14) consisted of the following adult (6 to 8 weeks old) mice: (1) t-PA−/− mice; (2) u-PA−/− mice; (3) u-PAR−/− mice; (4) plasminogen−/− mice; and (5) wild-type mice. In addition, newborn (p+7) u-PA−/−, t-PA−/−, and wild-type mice were studied. Mice were placed in a tightly sealed chamber under normobaric hypoxia (Fio2, 10%). Genotypic identical normoxic control mice were maintained in identical conditions in room air (Fio2, 21%).

**Hemodynamic Measurements**

The right ventricular systolic and diastolic pressures were measured in anesthetized mice (sodium pentobarbital, 60 mg/kg IP) by trans-thoracic puncture. Right ventricular pressure was measured continuously for 5 minutes with a pressure transducer (model AA 016, Baxter). Systemic arterial blood pressure was continuously measured over a 5-minute period by insertion of the needle into the abdominal aorta. Hemodynamic measurements were displayed on an oscilloscope (Pressure Amplifier 863, Elema) and analyzed on a PC-based computer program (WinDaq Software version 1.37, Dataq Instruments Inc).

**Blood Sampling and Hematocrit Measurement**

Blood samples were collected from the abdominal aorta and anticoagulated with EDTA (10 mmol/L). Hematocrit was measured with an automated cell counter (Abbott Cell-Dyn 1330 system).

**Measurement of Right Ventricular Hypertrophy**

The right ventricular free wall was separated from the left ventricle and septum under a dissecting microscope. The right ventricle and the left ventricle/septum were dried at 90° for 72 hours. Right ventricle and left ventricle plus septum were weighed separately. Results are expressed as ratio of right ventricle weight over left ventricle plus septum weight or right ventricle weight over body weight.

**Histology and Morphometric Analysis**

A cannula was introduced into the right atrium, and mice were perfused with 1% phosphate-buffered paraformaldehyde at 100 cm H2O pressure for 5 minutes. Subsequently, the trachea was cannulated and 1% phosphate-buffered paraformaldehyde was perfused at 30 cm H2O through the airways. The heart and lungs were removed en bloc, and the heart was separated from the lungs and the large vessels. The samples were cryoembedded or postfixed for 24 hours in 1% phosphate-buffered paraformaldehyde, dehydrated, and embedded in paraffin. Verhoeff–van Gieson elastic stains were performed on 4-μm sections. In addition, sections of the heart (7 μm) were used for sirius red staining and immunostaining of laminin, thrombomodulin, t-PA, u-PA, or matrix metalloproteinase-9 (MMP-9). In situ zymographic activity of t-PA and u-PA was performed with gel overlays on 7-μm unfixed cryosections.

Hypoxia-induced pulmonary vascular remodeling was assessed by two different methods. First, the peripheral vessel density (defined as the number of vessels per 100 alveoli) was determined. Peripheral arteries were defined as all vessels landmarked to airway structures distal to the terminal bronchioles. Nonmuscularized and partly or fully muscularized vessels were scored separately. Second, media thickness was determined by measuring the diameter between the internal and external elastic lamina.

Right ventricular myocyte hypertrophy was measured as the cross-sectional area of ~50 individual cardiomyocytes per heart in the right ventricle on laminin-stained sections to delineate the basement membrane. The number of subendocardial capillaries was counted on thrombomodulin-stained sections (to visualize endothelial cells) and expressed as number of capillaries per square millimeter. Collagen type I and III contents of the right ventricle were quantified on sirius red-stained sections.

**Statistical Analysis**

Results are presented as mean values ±SD. Statistical analysis was performed by ANOVA and subsequent Newman-Keuls test. A value of P < 0.05 was considered statistically significant.

**Results**

**Hemodynamic Measurements**

Adult wild-type mice that were exposed to 28 days of hypoxia showed a significant 1.8- to 2.7-fold rise in right ventricular pressure (Table 1). The right ventricular systolic...
TABLE 1. Right Ventricular Systolic and Diastolic Pressures, Mean Arterial Pressure, and Hematocrit in Mice Under Normoxic and Hypoxic Conditions

<table>
<thead>
<tr>
<th></th>
<th>RVSP, mm Hg</th>
<th>RVDP, mm Hg</th>
<th>MAP, mm Hg</th>
<th>Hematocrit, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wild-type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21% O₂ (n=6)</td>
<td>21±3.2</td>
<td>5.5±1.0</td>
<td>52±1.0</td>
<td>49±1.0</td>
</tr>
<tr>
<td>10% O₂ (n=7)</td>
<td>37±3.8*</td>
<td>15±3.7*</td>
<td>51±3.9</td>
<td>61±0.9</td>
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<tr>
<td>u-PA^{-/-}</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>21% O₂ (n=6)</td>
<td>21±2.6</td>
<td>6.1±2.1</td>
<td>53±4.1</td>
<td>49±1.1</td>
</tr>
<tr>
<td>10% O₂ (n=7)</td>
<td>24±3.1†</td>
<td>8.8±2.8†</td>
<td>51±2.5</td>
<td>61±1.1</td>
</tr>
<tr>
<td>u-PAR^{+/−}</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21% O₂ (n=6)</td>
<td>20±4.0</td>
<td>6.1±1.5</td>
<td>49±2.9</td>
<td>48±1.2</td>
</tr>
<tr>
<td>10% O₂ (n=7)</td>
<td>27±2.5†</td>
<td>12±1.7†</td>
<td>53±3.2</td>
<td>61±0.9</td>
</tr>
<tr>
<td>t-PA^{-/-}</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21% O₂ (n=6)</td>
<td>21±2.2</td>
<td>5.8±1.2</td>
<td>51±3.3</td>
<td>48±1.0</td>
</tr>
<tr>
<td>10% O₂ (n=8)</td>
<td>34±3.1*</td>
<td>15±2.6*</td>
<td>51±2.8</td>
<td>62±1.4</td>
</tr>
<tr>
<td>plg^{-/-}</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21% O₂ (n=7)</td>
<td>21±2.3</td>
<td>7.2±1.3</td>
<td>54±4.1</td>
<td>49±1.5</td>
</tr>
<tr>
<td>10% O₂ (n=8)</td>
<td>24±1.3†</td>
<td>6.3±2.7†</td>
<td>58±3.6</td>
<td>60±1.7</td>
</tr>
</tbody>
</table>

RVSP indicates right ventricular systolic pressure; RVDP, right ventricular diastolic pressure; and MAP, mean arterial pressure. Mean values±SD and statistical significance (P<0.05) are given.

*Normoxic vs hypoxic, †genotype vs wild-type.

and diastolic pressures were 37±3.8 mm Hg and 15±3.7 mm Hg, respectively, as compared with right ventricular systolic and diastolic pressures of 21±3.2 and 5.5±1.0 mm Hg in normoxic mice (P<0.01). In u-PA^{-/-} mice, no such increase in right ventricular pressure was seen. In contrast, t-PA^{-/-} mice showed a rise in right ventricular pressure in response to hypoxia that was fully comparable with that of wild-type mice. Mice with a deficiency in the u-PA receptor showed a partial but significant hypoxia-induced enhancement in right ventricular pressure. Plasminogen-deficient mice had no significant increase in right ventricular pressure in response to hypoxia. Hypoxia did not affect mean arterial blood pressure in any of the groups (Table 1). Hypoxia resulted in an increase in an identical hematocrit from 48.7±1.0% to 61.1±0.9%.

Right Ventricular Weight

In wild-type mice, hypoxia caused a 1.7-fold increase in the right ventricle/left ventricle + septum ratio and a 1.8-fold increase in the right ventricle weight/body weight ratio (Figure 1). In accordance with the right ventricular pressure measurements, u-PA^{-/-} and plg^{-/-} mice did not show any increase in right ventricular weight, whereas t-PA-deficient mice showed right ventricular hypertrophy that was comparable to wild-type mice. Hypoxia caused a significant increase in right ventricular weight in u-PAR^{-/-} mice; however, again this increase was more modest as compared with the increase in wild-type mice (RV/LV+S ratio in u-PAR^{-/-} mice 42±6% as compared with 51±5% in wild-type mice, P<0.05).

In newborn mice (10 days hypoxia), a similar pattern was observed (Figure 2). Both the right ventricle/left ventricle + septum ratio and the right ventricle weight/body weight ratio were markedly increased in wild-type mice (1.7- to 1.9-fold) and t-PA^{-/-} mice (1.6- to 2.0-fold) exposed to hypoxia. In contrast, u-PA^{-/-} mice did not show any significant increase in right ventricular hypertrophy in response to hypoxia. Total body weight was not different between hypoxic and normoxic mice of all different genotypes.

Pulmonary Vascular Remodeling

Hypoxia induced mild vascular rarefaction in the lungs of wild-type mice (Table 2). In wild-type mice exposed to hypoxia, a 29% reduction in nonmuscularized vessels and a 22% reduction in partly or fully muscularized arterioles were observed (P<0.05). Both u-PA^{-/-} mice and plg^{-/-} mice did not show such a reduction in vascular density in response to hypoxia. The hypoxia-induced rarefaction in t-PA^{-/-} mice was similar to that in wild-type mice. U-PAR^{-/-} mice showed an intermediate reduction in the number of arteries per 100 alveoli.

The increase in smooth muscle cells within the distal arterial walls, as reflected by the increase in media thickness, followed a similar pattern. In wild-type mice, hypoxia caused an ~2-fold increase in the ratio of media thickness over vascular diameter, which was similar in t-PA^{-/-} mice. Conversely, u-PA^{-/-} mice and plg^{-/-} mice did not show an increase in media thickness (Table 2 and Figure 3). In mice with a deficiency of the u-PA receptor, a significant increase in media thickness was observed, however, to a lesser extent.
Pulmonary vascular remodeling in response to hypoxia was somewhat more pronounced in newborn wild-type mice (data not shown) but was again completely absent in u-PA−/− mice.

There were no differences in pulmonary vascular density or media thickness between genotypes at normoxic conditions.

**Histological Analysis of Right Ventricular Hypertrophy**

Histological analysis revealed a hypoxia-induced increase in right ventricular cardiomyocyte size from 250±83 μm² to 340±68 μm² in wild-type mice, which was not present in u-PA−/− mice (Table 3). Also, the almost 2-fold increase in collagen content of the right ventricular wall in hypoxic wild-type mice was not seen in u-PA−/− mice (Figure 4 and Table 3). Right ventricular remodeling on hypoxia in wild-type mice was associated with a small but nonsignificant reduction in subendocardial capillary density (from 5200±210 per mm² to 4400±260 per mm²).

**Expression and Zymographic Activity of Plasminogen Activators and MMP-9 in Lung and Heart**

Immunostaining for u-PA revealed enhanced u-PA expression in lungs of hypoxic wild-type mice, in particular located near vascular smooth muscle cells (Figure 5). Zymographic analysis showed a 1.8±0.3-fold increase in u-PA activity in these lungs. In addition, there was increased MMP-9 expression (which might be seen as a candidate for u-PA–mediated plasmin formation) related to macrophages, in particular around the pulmonary vasculature. There was no major difference in the expression or zymographic activity of plasminogen activators in hearts from hypoxic mice as compared with hearts from normoxic controls.

**Discussion**

In this study, the role of the plasminogen/plasmin system in the pathogenesis of hypoxia-induced pulmonary hypertension

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**TABLE 2. Parameters of Pulmonary Vascular Remodeling in Hypoxic and Normoxic Adult Mice**

<table>
<thead>
<tr>
<th>Vascular Density</th>
<th>Wild-type</th>
<th>u-PA−/−</th>
<th>u-PAR−/−</th>
<th>t-PA−/−</th>
<th>plg−/−</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wild-type</td>
<td>21% O₂ (n=6)</td>
<td>2.4±0.2</td>
<td>4.0±0.3</td>
<td>6.1±1.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10% O₂ (n=7)</td>
<td>1.7±0.1</td>
<td>3.1±0.2</td>
<td>13±1.5</td>
<td></td>
</tr>
<tr>
<td>u-PA−/−</td>
<td>10% O₂ (n=7)</td>
<td>2.5±0.2*</td>
<td>4.0±0.2*</td>
<td>7.3±1.4†</td>
<td></td>
</tr>
<tr>
<td>u-PAR−/−</td>
<td>10% O₂ (n=6)</td>
<td>2.1±0.2</td>
<td>3.5±0.3</td>
<td>10±1.2*</td>
<td></td>
</tr>
<tr>
<td>t-PA−/−</td>
<td>10% O₂ (n=7)</td>
<td>1.8±0.2</td>
<td>2.9±0.2</td>
<td>13±1.9</td>
<td></td>
</tr>
<tr>
<td>plg−/−</td>
<td>10% O₂ (n=7)</td>
<td>2.7±0.1*</td>
<td>4.1±0.1*</td>
<td>6.3±1.5†</td>
<td></td>
</tr>
</tbody>
</table>

There are no differences between various genotypes under normoxic circumstances. Mean values±SD and statistically significant differences vs wild-type mice under hypoxia (*P<0.05; †P<0.01) are given.
and right ventricular hypertrophy was investigated. Chronic exposure to hypoxia resulted in increased pulmonary hypertension and right ventricular hypertrophy, associated with a marked remodeling of the pulmonary vasculature, characterized by a vascular rarefaction and an increase in media thickness of peripheral pulmonary arteries. However, u-PA and plg mice were resistant to these hypoxia-induced anatomical and functional changes, whereas t-PA mice responded to hypoxia in an identical manner as wild-type mice. Hypoxic u-PAR mice showed an intermediate response, which is significantly lower than wild-type mice. Hence, the plasminogen system is involved in hypoxia-induced pulmonary vascular remodeling and associated functional changes. In particular, u-PA appears to be of essential importance for the development of hypoxia-induced pulmonary hypertension. Because both u-PA and plg mice showed a similar lack of response to hypoxia, it may be assumed that u-PA acts by conversion of plasminogen to plasmin. The role of u-PA was further substantiated by the demonstration of upregulated u-PA expression and activity in hypoxic lungs. Ample evidence indicates that u-PA–mediated plasmin generation may play a pivotal role in tissue remodeling. It has been demonstrated in vivo that u-PA is essential for arterial neointima formation and adequate wound healing on vascular injury and for left ventricular remodeling after myocardial infarction. In contrast, t-PA, which is the major activator of plasma fibrinolytic activity, did not play an important role in the vascular remodeling and associated changes, which is in line with previous observations in other models. It should be noted that our observations do not exclude that the hypoxia-induced effects are related to a mediator other than hypoxia per se. For example, an increase in cardiac output and changes in hematocrit or vasoconstriction may contribute to the signaling that induced increased u-PA expression.

Although the exact mechanism of the hypoxia-induced changes in the pulmonary vasculature remains to be established, it can be assumed that it at least partly depends on the ability of cells to proliferate across anatomic borders, such as

**TABLE 3. Parameters of Right Ventricular Hypertrophy in Mice Under Normoxic and Hypoxic Conditions**

<table>
<thead>
<tr>
<th></th>
<th>Wild-Type Mice</th>
<th>u-PA/−/− Mice</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=5)</td>
<td>(n=5)</td>
</tr>
<tr>
<td>Cross-sectional diameter of cardiomyocytes, μm²</td>
<td>21% O₂: 250±40</td>
<td>21% O₂: 240±47</td>
</tr>
<tr>
<td></td>
<td>10% O₂: 340±68</td>
<td>10% O₂: 260±35*</td>
</tr>
<tr>
<td>Collagen contents of right ventricle, %</td>
<td>21% O₂: 7.8±1.8</td>
<td>21% O₂: 7.5±1.9</td>
</tr>
<tr>
<td></td>
<td>10% O₂: 14±2.1</td>
<td>10% O₂: 9.2±2.2*</td>
</tr>
<tr>
<td>Capillaries in subendocardium, per mm²</td>
<td>21% O₂: 5200±210</td>
<td>21% O₂: 5200±250</td>
</tr>
<tr>
<td></td>
<td>10% O₂: 4400±260</td>
<td>10% O₂: 5300±210</td>
</tr>
</tbody>
</table>

Mean values±SD and statistically significant differences vs wild-type mice (*P<0.05) are given.

**Figure 3.** Verhoeffs–van Gieson elastica staining of pulmonary arteries of wild-type (WT) mice (a and b) and u-PA/−/− mice (c and d). Wild-type mice show increase in media thickness on hypoxia (b); u-PA/−/− mice do not show signs of pulmonary vascular remodeling (d). In addition, in hypoxic wild-type mice, fragmentation of internal elastic lamina (IEL) and external elastic lamina (EEL) is shown (insert in b), which is not seen in u-PA/−/− mice (insert in d).
the elastic laminae. The present observation that u-PA−/− and plg−/− mice did not show hypoxia-induced fragmentation of the elastic membrane may explain the absence of pulmonary vascular remodeling in u-PA−/− deficient or plg-deficient mice. It is, however, not completely clear which mechanism can be held responsible for the hypoxia-induced rarefaction of pulmonary vessels, which was also less prominent in u-PA−/− and plg−/− mice.

Interestingly, hypoxia-induced pulmonary vascular remodeling was partly reduced in u-PAR−/− deficient mice as well. This observation indicates that the u-PA−/− effects in response to hypoxia are in part mediated by the u-PA receptor. Because u-PAR is expressed on smooth muscle cells and it has been shown that binding of u-PA to u-PAR may significantly affect smooth muscle cell adhesion to matrix proteins,34 u-PAR may play an additional supportive though not essential role in the u-PA−/− mediated response on hypoxia.

Our findings might have some relevance for the management of hypoxic pulmonary hypertension and right ventricular hypertrophy in patients because the murine hypoxia model has generally been accepted as a model for human hypoxic disease.5,35 Hypothetically, selective inhibition of u-PA activity or interference in the u-PA binding to the u-PA receptor (although to a lesser extent) might be of benefit for patients with pulmonary vascular disease caused by chronic hypoxia. At present, there is no specific therapy for this condition, and the occurrence of pulmonary vascular disease and secondary right ventricular hypertrophy and subsequent right heart failure is associated with considerable morbidity and mortality. However, further study in other models and in patients with hypoxic pulmonary hypertension is warranted before definitive conclusions regarding a potential therapeutic relevance of the present observations can be made.

Conclusions
Loss of the u-PA or plasminogen gene protects against the development of hypoxia-induced pulmonary hypertension, pulmonary vascular remodeling, and right ventricular hypertrophy. These observations indicate an essential role of the plasminogen system as a mediator of the direct or indirect adaptive responses to chronic hypoxia and in the occurrence of hypoxic pulmonary vascular disease.

Acknowledgments
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References

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