Angiopoietin-1 and Pulmonary Hypertension
Cause or Cure?
J.S. Rudge, G. Thurston, G.D. Yancopoulos

Our very existence depends on the air that we breathe, as well as the remarkable systems that have evolved to ensure that the oxygen we take into our lungs is efficiently delivered to the rest of the body via the bloodstream. When these systems begin to fail, life itself can become quite tenuous. Such failure occurs in pulmonary hypertension, a rare but serious disease whose pathophysiology remains obscure and increasingly controversial, as highlighted by two recent studies.1,2 Both studies focus on the potential role of angiopoietin-1 in this disease, but reach entirely antithetical conclusions.

The right side of the heart pumps blood into the lung vasculature, which consists of a low-resistance network that normally adjusts to increases in blood flow (eg, as necessitated by exercise) by dilation of its terminal arterioles to allow for increased flow without increasing resistance. In pulmonary hypertension, pulmonary arterial pressure is increased at rest and ratchets up dramatically with exercise, due to an inability to easily accommodate increased flow, imposing stress on the right ventricle. In response to the increased back pressure, the right side of the heart can hypertrophy to the point of failure. Current treatments are moderately effective at best. A study featured in this issue of Circulation Research,2 from the laboratory of Duncan Stewart, claims that angiopoietin-1 can have dramatic protective effects in an animal model of pulmonary hypertension. On the other hand, a recent article in the New England Journal of Medicine by Thistlethwaite and colleagues1 argues quite the opposite, depending on one’s view of the cellular basis of this disease.

The number of growth factors that specifically act on the blood vasculature is quite small and are limited to two families of factors known by their prototypical members—the vascular endothelial growth factor (VEGF) family and the angiopoietin family.3–5 Members of these families achieve their specificity based on the limited distributions of their receptors, which are expressed almost exclusively on the vascular endothelium. Both families act primarily via receptor tyrosine kinases, with those for the VEGFs termed VEGFR1, VEGFR2, and VEGFR3, and those for the angiopoietins termed Tie1 and Tie2. The enormous interest in these two families of growth factors results from the realization that they evolved to play very specific and critical roles in the vasculature, as initially suggested by their receptor distributions, and more recently confirmed by genetic knockouts of these factors and their receptors.3–5

While VEGF was discovered more than two decades ago,6 angiopoietin-1 has been identified much more recently,7 and thus its biological, pathological, and potential therapeutic roles are less well understood. One major emerging theme is that the VEGFs and the angiopoietins are not redundant, but instead play distinct and complementary roles, with the VEGFs acting early to initiate vessel growth, and the angiopoietins acting subsequently to promote vessel maturation and maintenance.5 Thus, while genetic ablation of VEGF-A causes embryonic lethality by preventing initial vessel outgrowth, knockout of angiopoietin-1 allows for initial vascular network formation, but these primitive vessels fail to mature, do not properly incorporate supporting smooth muscle cells, and begin to regress.8 A vessel maintenance or survival role for angiopoietin-1 has been supported by in vitro studies, which show that, although angiopoietin-1 differs from VEGF-A in that it cannot promote endothelial cell proliferation, it can indeed support endothelial survival.9,10 Interestingly, just as VEGF-A and angiopoietin-1 seem to play sequential and complementary roles during blood vessel development, recent studies indicate that VEGF-C/D and angiopoietin-2 similarly play sequential and complementary roles during lymphatic vessel development.11 The more recently described angiopoietin-2 also seems to play important roles during blood vessel remodeling, at least in some settings.11,12 In addition to the insights from genetic ablation studies, administration of angiopoietin-1 has suggested that it can lead to circumferential vessel growth in the absence of new vessel sprouting, and that it has opposing effects on vascular permeability compared with VEGF-A;11–13 ie, while VEGF-A promotes vessel leak, angiopoietin-1 seems to stabilize the vessel wall and prevent vascular leak.

So what is the rationale for studying angiopoietin-1 in pulmonary hypertension? It turns out that the rationale differs depending on one’s view of the cellular basis of this disease. One view, adopted by the Thistlethwaite group,1 is that the underlying cellular defect may involve abnormal activation and proliferation of vascular smooth muscle cells surrounding small pulmonary arteries and terminal arterioles, leading to their constriction and inability to dilate, thus resulting in

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947
Thistlethwaite group reports that angiopoietin-1 and associ-
ated activation of its Tie2 receptor is required for normal
endothelial function by promoting normal endothelial
smooth muscle interactions, which result in increased
effective resistance. The Stewart group begins with a very
different rationale and comes to a very different conclusion.
They focus on the possibility that pulmonary hyperten-
sion may be due to endothelial dysfunction. They start with
the notion that this could involve a disturbance in endothelial
vasodilator/vasoconstrictor balance, but they end with the
possibility that endothelial cell apoptosis may lead to vessel
loss that decreases the pulmonary vascular bed, leading to
increased resistance (Figure, see model 2). They exploit one
of the most intensively studied animal models of pulmonary
hypertension, in which rats are treated with monocrotaline (MCT),
and show that such treatment not only causes pulmonary hyper-
tension (with associated increases in right ventricular pres-
sure and size) and profound mortality but is associated with
reduction in endothelial NO synthase mRNA and endothelial
cell apoptosis in the microvasculature, particularly in the
critically positioned terminal arterioles. Administration of
angiopoietin-1 into this model, using a novel cell-based
delivery system designed to provide angiopoietin-1 to these
key sites, dramatically prevents mortality, improves all mea-
sures of pulmonary hemodynamics, and rescues endothelial
cells from apoptosis (Figure, see model 2).

So which rationale, and which set of conclusions, are most
relevant for patients suffering from pulmonary hypertension?
Thistlethwaite would argue that angiopoietin-1 (or Tie2)
blockers should be administered to such patients, while
Stewart would instead administer angiopoietin-1 itself. In
support of Thistlethwaite’s perspective, her conclusions were
mostly drawn from the analysis of human samples, in contrast
to those of Stewart and colleagues, which were based exclu-
sively on a toxin-generated animal model with unknown
relevance to the human disease. However, some of the
observations of the Thistlethwaite group run counter to
previous findings. For example, it has previously been shown
that angiopoietin-1 and activated Tie2 levels are normally
highest in the lung (eg,14), making it difficult to understand
why the Thistlethwaite group could only detect
angiopoietin-1 and activated Tie2 levels in lung samples from
pulmonary hypertension patients. In addition, in multiple
settings in which angiopoietin-1 has been administered to
rodents,13-15,19 smooth muscle hyperplasia was not noted in
the vascular beds examined. Furthermore, even in human
venous malformations in which Tie2 appears to be activated
by genetic mutation, resulting vascular lesions actually ex-
hibit decreased smooth muscle coverage.20 Altogether, these
previous findings seem to argue that while angiopoietin-1 and
Tie2 may be required for normal endothelial-smooth muscle
interactions, excess activation of this pathway need not lead
to smooth muscle hyperplasia. It cannot be ruled out, of
course, that such hyperplasia only occurs in particular vascu-
lar beds, or only after particular toxic challenges in these
beds. It should also be noted that it is possible that the
Thistlethwaite observation of increased angiopoietin-1 in
pulmonary hypertension is correct, but that this increase
reflects an insufficient compensatory response rather than a

Schematic representation of two differing models of pulmonary
hypertension. The models differ in terms of the cause of the
disease, as well as in the role of angiopoietin-1 in this disease.
Model 1 (on the left) assumes that the primary cellular defect
contributing to disease is smooth muscle cell hyperplasia, and
that this is caused by excess angiopoietin-1. Model 2 (on the
right) suggests that endothelial apoptosis underlies disease pro-
progression, and that this can be prevented by administration
of angiopoietin-1. See text for details.

increased pulmonary vascular resistance (Figure, see model
1). Supporting this view is the link between rare familial
cases of pulmonary hypertension and mutations in bone
morphogenic receptor type 2 (BMPR2), which, despite its
name, is thought to also regulate smooth muscle proliferation
and differentiation. The question asked by the Thistlethwaite
group is whether angiopoietin-1 might somehow provide a
link into the BMP pathway for the more common sporadic
forms of pulmonary hypertension, whose causes are unknown
but thought to result from hypoxia, left-sided heart failure,
use of anorexigenic drugs, and other toxic challenges. Their
rationale was that since angiopoietin-1 seems to normally
play a role in the developing vessel wall (it is made by smooth
muscle cells and acts on the endothelium), it might be
aberrantly involved in a disease with excessive smooth
muscle proliferation. Consistent with this possibility, the
Thistlethwaite group reports1 that angiopoietin-1 and associ-
ated activation of its Tie2 receptor cannot be detected in
normal human lung samples, but are highly elevated in lung
samples from patients suffering from pulmonary hyperten-
sion. Moreover, they find an associated decrease not in
BMPR2, but in BMPR1A, and further show that
angiopoietin-1 can repress BMPR1A levels when added to
cultures of pulmonary arterial endothelial cells. These
results lead them to conclude that excess angiopoietin-1 plays a
causative role in sporadic pulmonary hypertension by pro-
moting smooth muscle hyperplasia (Figure, see model 1),
specifically by linking it to downregulation of the BMP
pathway that has already been implicated in familial pulmo-
nary hypertension. Further support for this conclusion comes
from their own unpublished claims that administration of
angiopoietin-1 to rodents induces clinical and pathologic
pulmonary hypertension, including the smooth muscle hyper-
plasia characteristic of the human disease.

The Stewart group begins with a very different rationale
and comes to a very different conclusion. They focus on the
possibility that pulmonary hypertension may be due to
endothelial cell dysfunction. They start with the notion that
this could involve a disturbance in endothelial vasodilator/
vasoconstrictor balance, but they end with the possibility that
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cells from apoptosis (Figure, see model 2).
cause, thus reconciling these observations with those of the Stewart group.

Stewart’s perspective seems more consistent with previous findings that the angiopoietin-1/Tie2 system promotes endothelial survival and maintenance, and this perspective is also strengthened by the fact that it is derived from manipulative (as opposed to circumstantial) studies in which administered angiopoietin-1 is shown to be rather dramatically protective in an animal model. It is also intriguing that the vessels that might be most at risk in pulmonary hypertension, ie, the terminal pulmonary arterioles, are known to normally have the barest of smooth muscle coatings, which could make them more susceptible to toxic challenges and thus most likely to benefit from a survival factor such as angiopoietin-1. Unfortunately, the findings of the Stewart group fall short in that it is hard to know how relevant their model is with respect to the human disease. One could easily argue that MCT does indeed cause pulmonary hypertension by causing endothelial apoptosis, and that angiopoietin-1 can effectively protect against MCT damage by preventing endothelial death, but that this model may not reproduce all of the features of the human disease. Thus, it is uncertain whether angiopoietin-1 would be protective or beneficial to patients suffering from pulmonary hypertension.

So, is angiopoietin-1 cause or cure for this terrible disease? It seems as if more data are required, and the current controversy will certainly fuel more intense efforts to evaluate the angiopoietin-1/Tie2 pathway in additional models of pulmonary hypertension.

References


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