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Myeloid Targets for Pulmonary Arterial Hypertension: Time for Another Look

To the Editor:

We commend Yan and colleagues (1) on their elegant studies, which add to the accumulating evidence of a myeloid/bone marrow origin of pulmonary arterial hypertension (PAH). Using reciprocal bone marrow chimeras in immunocompetent *Bmpr2* mutant and wild-type mouse models, the authors identify bone marrow-dependent mechanisms in the muscularization of pulmonary arterioles and right ventricular systolic pressure elevation, without right ventricular hypertrophy. The findings are complementary to our previous xenograft study (2), in which hematopoietic stem cells derived from patients with PAH were transplanted into immunocompromised mice. Similar to the work by Yan and colleagues (1), hematopoietic stem cells from patients had fivefold higher engraftment, and transplant of stem cells from patients with *Bmpr2* mutations resulted in greater vascular smooth muscle cell hypertrophy than animals engrafted with mutation-negative PAH bone marrow stem cells. Just as important, prior study has shown that transplantation of serotonin 2B receptor-deficient bone marrow is protective against development of hypoxia-induced PAH (3), which indicates that myeloid stem cells can promote or block development of pulmonary vascular disease. Patients with PAH uniformly have an increase of hematopoietic progenitor and stem cell pools in the bone marrow compartment, even when there are no apparent blood abnormalities (2, 4). Intriguingly, patients with myeloproliferative malignancies, which are defined by

clonal stem cell expansion, have a high incidence of elevated right ventricular systolic pressure, providing complementary evidence that proliferative hematopoietic stem cells are closely related to pulmonary vascular disease (5). Altogether, these studies point to an abnormal hematopoietic progenitor/stem cell population that is an early step in the pathophysiology of PAH. Future studies are needed to define mechanisms via which hematopoietic progenitor/stem cells lead to PAH and whether this holds true for all subgroups of the disease. However, the anti-*c-Kit* drug imatinib, which targets stem cells, was effective in PAH (6), although complications limited its use. The recent work by Yan and colleagues (1), together with prior studies, provides a strong rationale to reconsider approaches that target hematopoietic progenitor/stem cells in the treatment of PAH. ■

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Reply: Expanded Role for Bone Marrow-derived Hematopoietic Stem and Progenitor Cells in Pulmonary Arterial Hypertension

From the Authors:

We agree with Asosingh and colleagues that there are now considerable data to indicate that the hematopoietic compartment of bone marrow contributes to the pathophysiology of pulmonary arterial hypertension (PAH). Initial direct evidence of this was provided by their seminal work, and our data further expanded and clarified their findings

(1, 2). It is important to point out here that our data do not suggest a diminished role for pulmonary vascular cells in PAH pathogenesis; they simply highlight the fact that bone marrow cells (BMC) are more important in PAH pathogenesis than previously believed.

The exact role of BMC in PAH has remained elusive in part because of (1) use of animal models such as Sugen, monocrotaline, or hypoxia, in which both BMC and microvascular cells were exposed to the stimuli, and thus precise dissection of the relative roles of BMC from microvascular cells could not be done; and (2) the short-term duration of the experimental design. For example, although monocrotaline or hypoxia can lead to rapid development of PAH in rodents, this does not mimic the long-term course of PAH in humans, in which the disease develops slowly over many years. Thus, genetic models of PAH are key to further delineating the role of BMC in PAH.

This work (Yan and colleagues [2] and Asosingh and colleagues [1]) also focuses on the potential of BMC as a therapeutic option in PAH. It is well known that PAH is refractory to most of the conventional pharmacological therapies. Lung transplantation effectiveness is limited owing to the number of donor organs available and the risks for graft rejection. Our combined work would suggest that better delineation of the role of BMCs in PAH, in particular BMCs of hematopoietic lineage such as hematopoietic stem cells, is needed to further clarify their potential use as a legitimate therapeutic approach. This is an important translational question with potential to affect patient treatment, because allogeneic bone marrow transplantation has been done for a long time for a number of hematological and genetic disorders, and the protocols are well established. ■

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Early-Life Exposure to Traffic-related Air Pollution and Lung Function in Adolescence

To the Editor:

I read the article by Schultz and colleagues (1), which concluded that exposure to traffic-related air pollution in infancy is negatively associated with FEV₁ at age 16 years, with great interest. It is well

known that the more physical activity, the larger the spirometric values; that is, physical activity could affect the lung function tests (2). In addition, obesity is also an important factor influencing spirometric values (3). In the study by Schultz and colleagues (1), however, physical activity and obesity of the enrolled subjects are not described in detail and seem to be ignored. It is quite possible that children with higher levels of exposure to traffic-related air pollution in infancy have less physical activity and higher rates of obesity than those with lower levels of exposure to traffic-related air pollution in infancy. These questions should be resolved in future studies. ■

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Reply

From the Authors:

We thank Dr. Song for his interest and questions regarding our article (1). Dr. Song highlights potential confounding for the association observed in our study between traffic and air pollution exposure during infancy and reduced FEV₁ at 16 years of age. Dr. Song discusses the possibility that children exposed to higher levels of traffic air pollution during infancy are less physically active and more obese, and therefore have reduced spirometric values in comparison with children with lower levels of traffic-air pollution.

Our cohort was recruited from different parts of Stockholm inner city and suburbs with traffic air pollution levels generally well below the World Health Organization guidelines (2) and within levels not hindering someone from performing exercise. However, a confounding effect might still be present, but mainly related to socioeconomic status. In Stockholm, the socioeconomic status is generally highest in the inner city, and gradually reduced in relation to distance to the city center. The opposite pattern is seen for traffic air pollution levels.

In our analyses, we adjusted for sex, age, height, weight, and municipality at birth. Socioeconomic position was investigated as a potential confounder, but no significant effect was observed. The addition of further adjustments for age-standardized body mass index levels (normal weight, overweight, and obese) or vigorous physical activity (self-reported in hours per week: 0–1.5, 2–4.5, 5–7.5, and >7.5)