plausible scenario is one that has the hygiene hypothesis (15) as its backdrop. The dual relationship between 17q21 variants and asthma risk may reflect the coevolution of an innate program that effectively prevents or counteracts the damaging effects of respiratory viruses, as long as protective environmental cues such as those that still persist in a traditional farm environment are available. The loss of these protective cues in the face of an ever-present viral threat could pave the way to the respiratory alterations characteristic of childhood asthma. It is noteworthy that the practical implications of 17q21-regulated interactions may well be far reaching, because the frequency of asthma-associated alleles in the general population approaches 50%.

Moving forward, the good news Loss and colleagues bring us is that if and when preventive treatments become available that leverage the asthma-protective mechanisms engaged by farm exposure, such treatments could be specifically targeted to, and would be especially successful in, the substantial proportion of children who carry the 17q21 asthma risk genotypes. Perhaps the day in which personalized medicine and the hygiene hypothesis will join forces is not so far away. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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The Role of Bone Marrow–derived Cells in Pulmonary Arterial Hypertension

What Lies Beneath?

Observations from diseased human tissues and experimental models have suggested that bone marrow (BM)-derived myeloid lineages may either drive or provide protection against the development of pulmonary arterial hypertension (PAH), and could be manipulated for therapy, but as of yet, no consensus exists on the causal or therapeutic role of BM-derived lineages in pulmonary vascular disease.

Troussard and colleagues originally described the syndrome of pulmonary venoocclusive disease and associated pulmonary

Supported by National Institutes of Health grant AR057374 (P.B.Y.), the John S. Ladue Memorial Fellowship at Harvard Medical School (I.N.), and a Fondation Leducq Transatlantic Network of Excellence Award (P.B.Y.).

hypertension as a known, albeit rare, complication of hematopoietic stem cell transplantation (1), providing the earliest suggestion that the BM compartment can adversely influence the pulmonary vasculature. In fact, compared with healthy control subjects, patients with PAH may have subclinical BM abnormalities and a higher number of circulating hematopoietic progenitors, including proangiogenic $CD34^+CD133^+$ lineages (2), but it has been unclear whether these changes are contributory or secondary to the disease process. Immunohistochemical studies of lung tissues obtained from patients with idiopathic pulmonary arterial hypertension (PAH) have identified c-kit^+, apparently BM-derived cells in the plexiform lesions and perivascular spaces of remodeled pulmonary arteries (3). Ablative BM transplant studies using labeled donor cells have demonstrated the accumulation of BM-derived cells in the pulmonary vascular lesions of hypoxic mice and monocrotaline-treated rats, giving rise in various studies to smooth-muscle α-actin-expressing myofibroblasts, endothelial-like cells, $CD45^+$ hematopoietic cells, and other lineages in the adventitia (4–6), demonstrating not only an association of BM-derived cells but also a possible contribution to vascular lesions of PAH. BM-chimeric immunodeficient mice engrafted with $CD133^+$ myeloid progenitors isolated from the BM of patients with PAH, but not healthy controls, developed several findings suggestive of pulmonary vascular disease, including angioproliferative remodeling and thrombosis *in situ* associated with right ventricular hypertrophy (7). Conversely, BM-derived endothelial-like progenitor cells from healthy animals infused without ablation into rats after monocrotaline treatment were found to engraft in the precapillary arterioles and attenuate the subsequent development of pulmonary hypertension (8). Testing the impact of ablative versus nonablative transplantation, Aliotta and colleagues found that infusion of whole BM combined with total-body irradiation ameliorated established pulmonary hypertension in monocrotaline-treated mice, an effect that was lost in the absence of total-body irradiation, whereas whole-BM infusion itself was sufficient to cause pulmonary hypertension and remodeling in previously healthy mice and was potentiated by total-body irradiation (9).

In this issue of the *Journal*, Yan and colleagues (pp. 898–909) demonstrate a pivotal role of BM-derived lineages in both causing and protecting from the development of pulmonary hypertension, while illustrating the contribution of dysregulated BMPR2 signaling in BM-derived lineages (10). The authors observed that transplantation of BM that expresses a premature termination codon mutant bone morphogenetic protein type II receptor transgene ($BMPR2^{R899X}$) into lethally irradiated control mice was sufficient to cause pulmonary hypertension, whereas engraftment of $BMPR2^{R899X}$ transgenic mice with control BM attenuated pulmonary hypertension. After essentially complete engraftment with donor BM, greater numbers of $CD3^+$ T cells and $CD68^+$ macrophages, both of donor origin, were found to be associated with remodeled vessels of mice receiving mutant BM. In contrast to previous BM transplant studies in pulmonary hypertension models, a BM contribution to smooth muscle or other vascular lineages was not observed. This study builds on previous work indicating the BM compartment may be abnormal in PAH and may harbor protective or disease-causing influences. This work amplifies the group's recent findings that global expression of the $BMPR2^{R899X}$ mutation is linked to systemic abnormalities in tissues beyond the pulmonary vasculature, including in BM-derived monocytic and tissue-resident macrophage lineages attributable to perturbed BMP signaling (11).

This study importantly demonstrates that BMPR2 loss-of-function mutations, identified in more than 70% of cases of heritable PAH and 10–25% of sporadic cases of idiopathic PAH, may exert some of their effects via myeloid and/or hematopoietic compartments (12). The inducible $BMPR2^{R899X}$ transgenic mouse and its derived BM cells used in the present study overexpress $BMPR2^{R899X}$, in contrast to individuals with heritable PAH, who typically express heterozygous loss-of-function BMPR2 alleles, frequently associated with nonsense-mediated decay, including the premature termination codon $BMPR2^{R899X}$ mutation (13). As the authors acknowledge, expression of the transgene may render signaling abnormalities or cellular defects that exist on a continuum with those present in the human haploinsufficient state, or may harbor other abnormalities resulting from exuberant expression of a dominant negative gene product that would normally be subjected to nonsense-mediated decay. However, the current study sets the stage for follow-up efforts to confirm similar BM-mediated causal or protective effects in other robust genetic models of pulmonary hypertension that recapitulate heritable PAH syndromes in man, including caveolin-1 knockout mice (14), and in heterozygous $BMPR2^{R899X}$ knock-in mice that develop modest spontaneous pulmonary hypertension (15).

The current findings lend significant weight to a causal and protective role of BM-derived lineages in PAH. These reciprocal transplant experiments might suggest that ablative transplantation with healthy or genetically normal bone marrow might be explored as potential corrective therapy in very severe PAH or heritable PAH, respectively. Translatability of an allogeneic BM transplant approach might be limited, however, when moving from syngeneic mouse strains to outbred humans, particularly given the concern that graft-versus-host disease might contribute to pulmonary venoocclusive disease associated with hematopoietic stem cell transplants, in addition to conditioning regimens themselves, which could still complicate the transplantation of matched-related or autologous, genetically corrected BM. Moreover, the discrepant results in prior studies examining the protective versus injurious role of engrafted BM underscore the complexity of the BM as a heterogeneous source of multiple progenitor populations whose effects on recruitment to sites of injury are certainly lineage dependent. The incomplete rescue of pulmonary hypertension in $BMPR2^{R899X}$ mutant mice by wild-type marrow leaves open the possible impact of this mutation in other populations not necessarily in equilibrium with the BM. For example, lineage-specific effects of the BM are likely to be modified further by tissue-resident antigen presenting and inflammatory cells such as lung-resident macrophages, a population that develops and regenerates independent of BM monocytes and serve as mediators of airway disease (16), and that could contribute to pulmonary vascular disease, a concept that could be tested via tissue-specific ablation. Precise delineation of the most restricted and protective BM- or non-BM-derived hematopoietic, myeloid, or monocytic lineages and their downstream mediators could help to translate the valuable new insights gained from the current studies into viable therapeutic approaches. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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