More than a third of the nation's population lives in areas that exceed the current ozone standard (6). As healthcare providers and scientists, the members of the American Thoracic Society should urge the EPA to carefully consider the increasingly strong epidemiologic evidence that long-term exposure increases the risk of cardiopulmonary mortality when the agency next evaluates the current NAAQS for ozone. ■

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Remember Me? The Bone Marrow in Pulmonary Fibrosis

Idiopathic pulmonary fibrosis (IPF) is a progressive, fibrosing disorder that is primarily confined to the lungs, in contrast to several other nonidiopathic forms such as those associated with connective tissue diseases. This does not exclude a participation of distant organs, in particular the bone marrow, in the development and/or progression of IPF. Despite early excitement of the potential for bone marrow–derived cells to give rise to structural cells of the lung (1–3), this concept of engraftment and differentiation has evolved into an understanding of the more plausible paracrine functions of bone marrow–derived cells in the host repair response to lung injury (4–6).

In this issue of the *Journal*, Nakashima and colleagues (pp. 1032–1044) (7) report exploring the hypothesis that low-level injury to the lung insufficient to cause fibrosis (the "first hit") leads to a priming of the bone marrow that results in a more robust fibrotic response to a second, more severe fibrogenic injury. With a series of elegant bone marrow chimeric studies in mice, the authors show that recipient mice subjected to bleomycin-induced lung injury develop worse fibrosis with donors previously subjected to a low-dose, nonfibrogenic lung injury. Further, their studies support a requirement for the immunomodulatory glycoprotein, B7-homolog 3 (B7H3, CD276) and the receptor for IL-33, ST2 (mouse homolog of the IL-1 receptor-like 1 gene), in mediating the priming effect on bleomycin-induced lung fibrosis. With corroborative *ex vivo* studies, the authors surmise that B7H3 exacerbates experimental lung fibrosis by activating (recruiting) a monocytic progenitor population in (from) the bone marrow and skewing of the immune response to a T-helper cell type 2 phenotype. The potential clinical relevance of these studies is supported by the observation that the soluble form of B7H3, sB7H3, is elevated in plasma of human subjects with IPF and in BAL fluid during acute exacerbations.

This innovative study provides conclusive evidence that changes in the bone marrow resulting from remote subclinical injury to a distant organ (the lung, in this case) may have a priming effect on the subsequent host response to injury in a mammalian model system. This concept of immunological memory has classically centered around antigen-specific memory in adaptive immune cells such T and

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B cells but has recently been expanded to include antigen nonspecific memory involving innate immune cells such as natural killer cells and group 2 innate lymphoid cells (ILC2) (8). Although Nakashima and colleagues focused their attention on this "memory-like property" of ILC2 cells, it is important to recognize that antigen nonspecific memory may be more ubiquitous and involve other innate immune cells, as well as structural cells within an injury-challenged organ. Indeed, prolonged memory encoded in skin epithelial stem cells after an acute inflammatory stimulus enables these cells to more efficiently restore barrier function after a subsequent insult (9). Interestingly, B7H3 is ubiquitously expressed in both immune and nonimmune cells, with high expression in epithelial cells (10). Thus, the specific cell type or types involved in the encoding of memory to fibrogenic injury need to be ascertained. Furthermore, the molecular mechanisms of immunological memory are not well understood. Although such memory encoded in immune cells such as T lymphocytes in response to infectious agents has been well appreciated for decades, similar effects of the host response to noninfectious injuries is less well appreciated. In either case, the origins of this memory have remained unclear; interestingly, recent studies implicate the epigenetic, DNA methylation–dependent differentiation of memory T cells from effector T cells (11, 12).

The study by Nakashima and colleagues indicates a requirement for B7H3 in the more severe fibrotic response to a second insult; however, it is not known whether this is a result of signaling by the membrane-bound form of the protein or its soluble form. Because the soluble form of such receptors can function as potential decoy molecules, the precise role of these spliced variants in the memory responses to noninfectious lung injuries need to be clarified. Thus, although the finding of sB7H3 in the plasma and BAL fluid of human subjects with IPF is intriguing, their precise role in disease pathogenesis deserves further investigation.

From a translational perspective, this study provides insightful clues to developing improved and testable models of experimental fibrosis that may more closely resemble the human disease. A one-time bleomycin injury to the lung elicits a resolving fibrosis response in young C57BL/6 mice (13–15). However, repetitive injury with bleomycin induces a more persistent fibrosis in these mice (16). Although the study by Nakashima and colleagues did not examine the persistence of the fibrotic response in their 2-hit model, it is plausible that such models may produce a more durable response that may be more amenable to study of disease pathogenesis and provide more robust and reproducible platforms for preclinical drug testing. ■

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