Tissue Fibrocytes Are a Subpopulation of Macrophages

To the Editor:

The term “fibrocyte” was coined by Bucala and colleagues in 1994 to describe a cell that appeared in long-term cultures of adherent leukocytes (1). Many subsequent reports have described apparently novel bone marrow–derived cells, termed fibrocytes, that circulate in the bloodstream in humans and appear at sites of tissue fibrosis. However, purification and precise phenotypic analysis (including microscopy) of circulating human fibrocytes has not been reported. In their elegant study of fibrocytes in the *Journal*, Madala and colleagues demonstrate that bone marrow–derived cells that express the leukocyte marker CD45 are able to infiltrate fibrotic lung and modulate fibrosis in the mouse (2). These cells expressed the myeloid marker CD14 along with CD44 and were able to synthesize collagen 1, and they regulated proliferation of resident fibroblasts. These fibrocytes described by Madala and colleagues have remarkably similar characteristics to monocyte-derived macrophages. CD14-positive monocytes are produced in the bone marrow, circulate in the blood, and are recruited into tissues where they differentiate into macrophages. Tissue macrophages exhibit great heterogeneity with many different forms and functions, with roles in tissue homeostasis and responses to injury; in particular, they can proliferate, synthesize collagen, and regulate tissue fibrosis (3–6).

The results of Madala and colleagues support the idea that tissue fibrocytes are a subpopulation of macrophages. If so, then reference to fibrocytes as a novel cell type is unhelpful. Future studies that incorporate cell sorting and careful analyses of morphology and function would help resolve this uncertainty. ■

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Reply: Tissue Fibrocytes Are a Subpopulation of Macrophages

We thank Dr. Simon for his interest in our article, and strongly support the conclusion to consider careful analyses of morphology and functions of tissue macrophages (1). Indeed, tissue monocytes that migrate from the circulation can differentiate into one of a number of cell types, including macrophages, osteoclasts, and dendritic cells (2). Monocytes have been shown to differentiate into fibrocytes under *in vitro* culture conditions (3). However, it is unknown whether this phenomenon is true *in vivo*, and in particular, under fibrogenic microenvironment conditions. The development of fibrocytes has been shown to be regulated by signaling through the Fc γ receptor and augmented in the presence of fibrogenic cytokines, such as IL-4 and IL-13 (4), whereas activators of innate immune responses, such as serum amyloid P and Toll-like receptor 2 ligands, are known to inhibit transformation of CD14⁺ monocytes to fibrocytes (5). It is also unknown whether macrophages within the mononuclear phagocyte pool of the lung can contribute to the fibrocyte cell population. A major problem in distinguishing macrophages and fibrocytes lies in the fact that they express common cell surface markers, as they both arise from common myeloid precursors. The cell surface marker, F4/80, does distinguish the majority, but not all, of the subsets of cells within the macrophage pool (2, 6). However, our flow cytometry data suggest that transforming growth factor- α -induced fibrocytes isolated from the fibrotic lung tissue did not express F4/80 (data not shown). Therefore, future studies are needed to further explore the morphology and functions of tissue macrophages to reveal the extent to which these cells contribute to the fibrocyte cell population, and thus, to pulmonary fibrosis. ■

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