Molecular Medicine

Fibrocytes at 20 Years

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Since the discovery of the "fibrocyte" as a collagen-producing leukocyte in the 1990s, our knowledge of the physiologic and pathologic role of this unique cell population has grown steadily. Fibrocytes traffic to sites of injury during the earliest phase of the innate immune response and exhibit both the inflammatory features of macrophages and the tissue remodeling properties of fibroblasts. Fibrocytes are distinguished by the simultaneous expression of CD34 or CD45 and collagen. Although these cells were first described in the context of wound repair, accruing evidence supports their central participation in the pathogenesis of different fibrosing disorders. Reliable methods for the enumeration of circulating fibrocytes have been developed, which indicate the utility of such measurements in disease prognosis. Ongoing research is focusing on the molecular signals that influence fibrocyte migration, proliferation and function in the context of normal physiology and pathology. Fibrocyte-directed therapies also have entered clinical testing for the amelioration of aberrant wound repair and pulmonary fibrosis.

The fibrocyte is a circulating connective tissue cell that was described in the inaugural issue of *Molecular Medicine*. I was invited to submit this report by the journal's late cofounder, Dr. Ken Warren, who made it his business to stay abreast of unpublished research. Ken promised a timely review and the potential to highlight the distinctive starfish-like appearance of fibrocytes on the journal's first cover (Figure 1).

This published report was prompted by the discovery that within subcutaneous wound chambers, one could observe at the earliest stages the entry of remarkable numbers of spindle-shaped, fibroblast-like cells. Phenotypic analysis of these cells by flow cytometry and gene expression studies revealed the unexpected presence of both stromal and myeloid characteristics. We called these distinctive cells "fibrocytes" in recognition that they produce collagen (*fibro*) and circulate (*cyte*). Fibrocytes now are recognized as mesenchymal cells that arise from circulating monocyte precursors (Figure 2) (1).

Despite initial resistance to the heterodoxy that connective tissue cells "circulate," the notion of a circulating fibroblast-like precursor cell gained traction as fibrocytes were identified under more and more circumstances. It nevertheless should be acknowledged that there is a descriptive literature that goes back as far as James Paget's *Lectures on Surgical Pathology* to support the idea that circulating mononuclear cells can transform themselves into connective tissue elements (2).

The last 10 years have witnessed a more widespread acceptance of the fibrocyte and a remarkable expansion in the number of physiologic and pathologic conditions in which these cells partici-

Figure 1. The inaugural issue of *Molecular Medicine*. Published in November, 1994.

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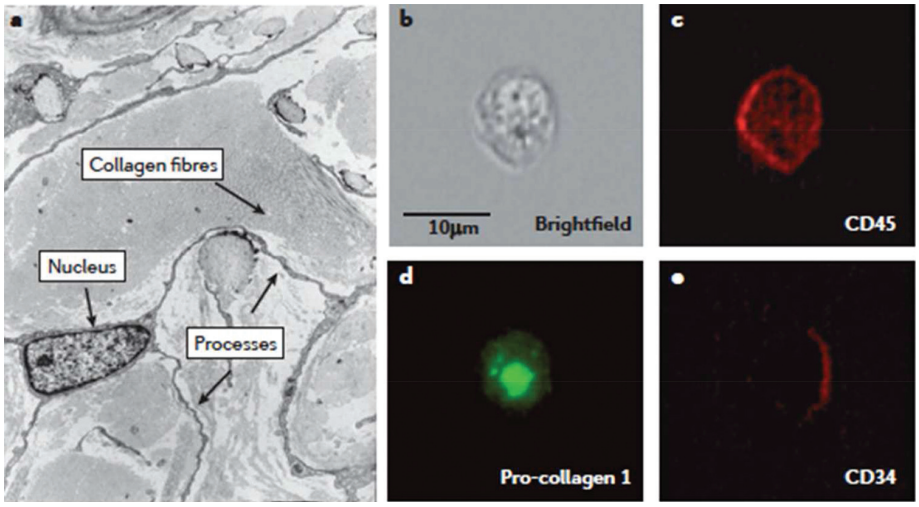

Figure 2. (A) Electron micrograph of a fibrocyte from a patient with accelerated dermal fibrosis due to nephrogenic sclerosing fibrosis. (B–E) Brightfield and successive confocal immunofluorescence images of a fibrocyte in normal human circulation illustrating its defining characteristics. From Reilkoff *et al.* (1).

pate, including normal and aberrant wound repair (3,4), different organ-specific fibrosing disorders (5–7), systemic fibroses (8,9) and novel roles in autoimmunity (10,11). Fibrocytes appear to participate broadly in the innate response to injury or tissue invasion, where they exhibit functional features of macrophages, including antigen presentation, together with the tissue remodeling properties of fibroblasts (12). Whereas fibrocytes normally comprise only a fraction of circulating leukocytes, increased numbers can be found in the circulation during pathologic disorders that are characterized by both chronic macrophage-driven inflammation and persistent fibroblast activation (13). In circumstances where access to subjacent connective tissue may be anatomically limited, circulating fibrocytes may play an especially vital role in the ultimate repair and remodeling response of the injured site.

Distinct inflammatory stimuli have been identified to mediate the differentiation, trafficking and accumulation of fibrocytes in fibrosing conditions associated with unresolved inflammation and tissue damage, and that may develop as a consequence of persistent infection, autoimmunity or ischemic tissue injury. Perhaps the most important factor leading to the expansion of fibrocyte biology over the last 10 years was the identification of fibrocytes as important cellular constituents of pulmonary pathology, initially in asthma (14), but subsequently in interstitial lung diseases and idiopathic pulmonary fibrosis (5). The enumeration of peripheral blood fibrocytes has been validated as a prognostic marker in pulmonary fibrosis, and such measurements may have application in other disorders as well (15). There has been significant recent insight into the differentiation, trafficking and effector functions of fibrocytes, with continued developments in our understanding of the mediators that drive fibrocyte differentiation (16,17). Persistent T-cell activation is a prominent feature, albeit by incompletely understood pathways, of several fibrosing disorders, and it has become evident that the precise context of T-cell activation influences fibrocyte differentiation in target organs (18).

Fibrosis is a final common pathway for many chronic diseases for which there are inadequate therapies. These conditions encompass the many viral and granulomatous infections that afflict much of the world's population, and they include the diverse etiologies of interstitial lung diseases, cirrhosis, chronic kidney disease and atherosclerosis. There are no effective therapies to restrict progressive end-organ damage and obliteration by fibrosis. Research translation has continued as an important focus of *Molecular Medicine* since its founding, and it is notable that the initial description of fibrocytes has spawned a specific fibrocyte-directed therapy that is now in clinical evaluation. In 2003, Gomer and colleagues reported on the discovery of serum amyloid P as an endogenous circulating inhibitor of fibrocyte differentiation (17,19). Produced recombinantly, serum amyloid P (also known as pentraxin-2 or the drug PRM-151) has a therapeutic action by its provision of a partial agonistic signal to Fcγ receptors, leading to a differentiation block in target monocytic precursors (20). PRM-151 has shown remarkable therapeutic activity in several preclinical models of organ-specific fibroses, including those in the lung, heart, skin and kidney, and it has advanced to phase II clinical testing in post–glaucoma surgery scarring and in idiopathic pulmonary fibrosis. As such, the inaugural report by *Molecular Medicine* of fibrocyte discovery has led to a lasting legacy of new science and a promising therapeutic target now in advanced clinical evaluation.

DISCLOSURE

R Bucala is a former member of the Scientific Advisory Board of Promedior, Inc., which is developing PRM-151 for clinical application, and owns equity as compensation (<$10,000).

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