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Theme Issue Article

The role of circulating mesenchymal progenitor cells (fibrocytes) in the pathogenesis of fibrotic disorders

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Summary

Fibrocytes are bone marrow-derived mesenchymal progenitor cells that express markers of leukocytes, haematopoietic progenitor cells, and fibroblasts. They play a pivotal role in tissue remodelling and fibrosis in both physiologic and pathologic settings. Fibrocytes are unique in that they are capable of differentiating into fibroblasts and myofibroblasts, as well as adipocytes. In this review we will present data supporting the critical role they play in the pathogenesis of chronic inflammatory fibrotic diseases of the lungs, heart and vasculature.

Keywords

Chemokines, collagens, wound healing

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Introduction

Circulating fibrocytes, first identified in 1994 in the context of wound repair (1), are unique bone marrow-derived mesenchymal progenitor cells that are defined by their growth characteristics and surface phenotype: They express markers of leukocytes, haematopoietic progenitor cells, and fibroblasts (2) as well as a number of others markers including chemokine receptors and adhesion molecules (3, 4) (Table 1). Fibrocytes participate in tissue remodelling by producing extracellular matrix proteins (collagen I, collagen III, and vimentin), and by secreting matrix metalloproteinases (5). Moreover, fibrocytes are an important source of inflammatory cytokines, chemokines and growth factors that provide important intercellular signals locally within the tissue (4, 5): fibrocytes isolated from a wound chamber model were found to express mRNA for interleukin (IL)-1β, IL-10, tumour necrosis factor (TNF)-α, monocyte chemotactic protein (MCP), macrophage inflammatory protein (MIP)-1α, MIP-1β, MIP-2, platelet-derived growth factor (PDGF)-A, transforming growth factor (TGF)-β1, and monocyte colony-stimulating factor (M-CSF). Some of the chemokine signals that recruit fibrocytes into sites of tissue injury and propagate the fibrotic response have also been identified (5). Fibrocytes can differentiate into more fibroblasts and myofibroblasts, as well as adipocytes (6, 7). These cells are important mediators of antigen-specific immunity (8), wound repair (1), and pathologic fibrosis in response to local inflammation (9). These unique cells have become the focus of research efforts that encompass a wide variety of focal and diffuse fibrosing disorders including those localized to the skin (10), lungs (11), pancreas (12), kidney (13) and bladder (14); and the more diffuse involvement seen in tumor metastases, intimal hyperplasia (15), the fibrous cap in human carotid artery plaques (16), and in animal models of atherosclerosis (17). In this review, we will concentrate on the data supporting the pivotal role of fibrocytes in the pathogenesis of chronic inflammatory and fibrotic disorders of the lung, heart and vasculature.

The circulating fibrocyte

The circulating fibrocyte was first described in 1994 (1): in an experimental model of wound repair, within one day following injury, 10% of the cells in the wound chamber were spindle-shaped and expressed collagen, procollagen, and CD34. The concept that these cells were circulating came from the logistical observation that their appearance in the wound chamber was much faster than would be expected by entry of fibroblasts from the surrounding skin, since the fibroblasts would have to traverse the permeable plastic layer, enter the wound chamber, and begin collagen production (13). These spindle-shaped cells bore markers of connective tissue cells, but not of monocytes, macrophages, endothelial cells, or epithelial cells. Thus the word fibro-

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cyte (a term combining fibroblast with leukocyte) was coined for this circulating fibroblast progenitor that produced collagen and expressed the haematopoietic marker CD34 (13). Morphologically, fibrocytes exhibit prominent cell surface projections on scanning electron microscopy making them distinct from leukocytes (1).

In addition to promoting fibrosis, fibrocytes have also been shown to play an important role in the recruitment and activation of T cells as antigen-presenting cells (8). Moreover, fibrocytes are involved in angiogenesis *in vivo* (18), and secrete many inflammatory cytokines, chemokines and growth factors that mediate fibrosis (3, 5). Fibrocytes comprise 0.1–1% of the nucleated cells in the peripheral blood in healthy hosts (3, 4, 9), and have been found in a variety of tissues under both physiologic and pathologic states (3).

In the context of physiologic and pathologic fibrosis, tissue fibroblasts and myofibroblasts are classically thought to derive from resident fibroblast that proliferate and express constituents of the extracellular matrix in response to tissue injury (19–21). However, there are two contemporary theories that have been proposed. The first theory states that tissue injury induces epithelial cells to transition to a mesenchymal phenotype (the fibroblast/myofibroblast), that subsequently contributes to fibroproliferation (20, 22). The second theory, and the focus of this review, is that circulating fibrocytes (from bone marrow-derived progenitor cells) home and extravasate into sites of tissue injury, differentiate into fibroblasts/myofibroblasts, and contribute to the generation of extracellular matrix during fibroproliferation (1, 3, 23). We will present supporting evidence for the bone marrow origin of fibrocytes.

Bone marrow origin of fibrocytes

Fibrocytes express markers of haematopoietic cells (CD45, major histocompatibility complex II, and CD34) and stromal cells (collagens I and III, and fibronectin) (1, 4, 9, 23–28). They do not, however, express T-cell markers (CD3, CD4, and CD8), B-cell markers (CD19), the IL2 receptor chain CD25, the low-affinity Fc gamma receptor III (CD16), and myeloid markers (CD14 and non-specific esterase) (1, 3, 4, 9, 23, 29). Since the expression of CD34 by the fibrocyte has been shown to decrease over time (both in culture and *in vivo*) depending on the inflammatory milieu (13), the co-expression of collagen production and the other haematologic markers (such as CD45) are frequently used to identify fibrocytes: early in culture, fibrocytes are associated with expression of CD34, CD45, collagen I, and vimentin. After exposure to TGF-β or endothelin, fibrocytes differentiate into myofibroblast-type cells resulting in expression of α-smooth muscle actin, and loss of CD34 and CD45 expression (4, 9, 29, 30). Thus, while the classic markers for circulating fibrocytes are CD45, CD34, collagen I, and vimentin, this definition likely underestimates the true number of tissue fibrocytes.

Evidence suggests that fibrocytes can differentiate from CD14+ peripheral blood monocytes that express the receptors for the Fc portion of IgG, CD64, and CD32 (26–28). Circulating fibrocytes may be present in a subset of CD14+ CD16– monocytes that carry the chemokine receptor, CCR2, on their surface (31, 32). At the time of tissue injury this monocyte subset is released from the bone marrow into the peripheral blood and migrates to inflamed sites via a CCR2-mediated pathway (31, 32). Human fibrocytes may represent an intermediate stage of differentiation of this monocyte subset into mature fibroblasts and myofibroblasts in tissue (33). This hypothesis is supported by the fact that fibrocytes express the major histocompatibility complex class I and class II, CD80, CD86 (1, 8, 27, 28, 34), exhibit antigen-presenting activity (8), and activate CD4+ and CD8+ lymphocytes (8, 34); but do not express markers of monocyte-derived dendritic cells such as CD1a, CD10, and CD83.

Fibrocyte differentiation

In tissue, differentiating fibrocytes loose CD14 and CD45 expression, and upregulate markers that are no longer expressed by mature monocytes such as CD34 (6, 15, 23, 27, 28, 35). The differentiation of fibrocytes into fibroblasts, myofibroblasts or adipocytes *in vivo* has been under studied. While there is no direct evidence for differentiation *in vivo* of the fibrocytes to myofibroblast or adipocytes, there is significant indirect evidence *in vitro* for this to occur based on findings for gene and protein expression, and functional changes compatible with the phenotype of either an alpha-smooth muscle actin/ myofibroblast-like cell and adipocyte (28, 29). For example, the differentiation of fibrocytes into myofibroblasts is augmented in the presence of TGF-β or endothelin-1, and results in cells that produce fibronectin and collagen, and express the myofibroblast marker α-smooth muscle actin (3, 4, 9, 23, 29). In a wound repair model, bone marrow transplantation from GFP-transgenic animals to wildtype animals showed that the cells in the wound co-expressed GFP and α-smooth muscle actin, suggesting that the myofibroblasts were derived from the bone marrow (36). It has been shown that in addition to fibroblasts and myofibroblasts, fibrocytes can differentiate into other mesenchymal cell types: fibrocytes differentiated into adipocytes *in vitro* and *in vivo*, through a process that is PPAR-γ-dependent and inhibited by TGF-β (6). Recently, it has been shown that the pro-fibrotic cytokines IL-4 and IL-13 promote fibrocyte differentiation from CD14+ peripheral blood monocytes without inducing proliferation, whereas the anti-fibrotic cytokines IL-12 and interferon (IFN)-γ inhibit fibrocyte differentiation (37): IL-4, IL-13 and IFN-γ were found to regulate fibrocyte differentiation through a direct effect on monocytes, whereas IL-12 was found to have an indirect effect possibly through CD16+ NK cells. These findings taken together with the previous studies suggest that fibrocyte differentiation is influenced by a complex profile of cytokines, chemokines and plasma proteins within the area of tissue injury.

Fibrocyte trafficking

According to the disease process and organ involved, fibrocytes can use different chemokine ligand-receptor pairs for tissue homing. Human fibrocytes express several chemokine receptors, including CCR3, CCR5, CCR7, and CXCR4; in contrast, mouse fibrocytes express CXCR4 and CCR7, but also CCR2 (4, 9, 23, 38). Fibrocyte migration into wound sites can be quantified by labeling the cells ex vivo with a fluorescent dye: if chemokines that bind to CCR7 or CXCR4 (such as CCL21 and CXCL12) are injected intradermally, fluorescently labeled fibrocytes were found to migrate to the site of injection (23).

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The CXCR4-CXCL12 axis plays an important role in the homing of bone marrow-derived progenitor cells (39): CXCR4 is an important chemokine receptor in stem cell trafficking, and the differential expression of CXCL12 in tissues creates the gradient required for trafficking of CXCR4+ cells. Although an early study reported little chemotaxis of fibrocytes to CXCL12 (23), our group detected substantial chemotaxis *in vitro* and *in vivo* of these cells to CXCL12 (9) and consider the earlier results to be due to methodological differences between laboratories. In a mouse model of pulmonary fibrosis, fibrocytes were found to express CXCR4 and migrate in response to CXCL12 in vitro and in the setting of bleomycin-induced pulmonary fibrosis *in vivo* (9, 25). In the bleomycin model, antibody-mediated neutralization of CXCL12 resulted in reduced fibrocyte recruitment to the lung and decreased collagen deposition (9). The CXCR4-CXCL12 axis also appears important in the trafficking of human fibrocytes in the setting of lung fibrosis: in a study of patients with fibrotic interstitial lung disease, the numbers of CD45+, collagen I+, CXCR4+ fibrocytes were an order of magnitude higher than in healthy controls. Moreover, the CXCL12 ligand expression was also markedly elevated in the lung and plasma of patients with lung fibrosis (11). In a study of patients with idiopathic pulmonary fibrosis (40), immunofluorescence and confocal microscopy of fibrotic lung tissue using CXCR4 stained more fibrocytes than combinations using CD34 or CD45RO. CXCL12 was significantly increased in the plasma of patients with idiopathic pulmonary fibrosis compared to healthy controls; and was detectable in the bronchoalveolar lavage fluid in 40% of the patients with pulmonary fibrosis (but not in controls). Moreover, CXCL12 was strongly expressed by alveolar epithelial cells within the lung. Results of these human studies, underscores the importance of chemokine-mediated fibrocyte influx in organ fibrosis, and indicate that circulating fibrocytes, likely recruited through the CXCR4-CXCL12 axis, may contribute to the expansion of the fibroblast/myofibroblast population in idiopathic pulmonary fibrosis.

Fibrocytes and diseases of the lung, heart, and vasculature

Animal models of lung fibrosis (9, 41–44), atherosclerosis (17), intimal hyperplasia (15), and ischemic cardiomyopathy (45) have provided evidence of a causal link between the accumulation of fibrocytes at sites of tissue injury and tissue remodelling.

Focal and diffuse fibrosis of the lung parenchyma

Tissue regeneration and repair is critical to the recovery of tissue from injury, and aberrant remodelling is a key feature of many chronic fibrosing diseases, including chronic lung infections and interstitial lung disease. Lung fibroblasts and myofibroblasts, originally thought to be derived exclusively from resident lung fibroblasts (19, 21, 46), can be derived from tissue-resident mesenchymal stem cells (47) and bone marrow-derived precursor cells (1, 9, 23). Animal models suggest that fibroblasts can also differentiate from pulmonary epithelial cells (i.e. epithelial-mesenchymal transition) (48) and fibrocytes (3, 4, 9, 23, 29).

Fibrotic lung diseases are a large group of disorders characterised by varying degrees of inflammation and fibrosis of the lung parenchyma (49). The clinical course is usually one of progressive replacement of lung tissue with scar tissue, and concomitant clinical deterioration. In some of these disorders the underlying etiology is known, while in others, the etiology is still unknown. Among these fibrotic lung disorders, idiopathic pulmonary fibrosis is the most common and is defined as the histopathologic finding of usual interstitial pneumonia in the absence of other recognizable causes (49).

Several lines of evidence support the role of circulating fibrocytes in the development of lung fibrosis (50). In general, the interest in studying the potential role of fibrocytes in the pathophysiology of lung fibrosis stems from the well-known characteristics of fibrocytes themselves including: 1) fibrocytes can differentiate into fibroblasts and myofibroblasts (3, 4, 9, 23, 29); 2) fibrocytes can produce cytokines that induce collagen deposition (3–5, 9, 23, 29); 3) fibrocytes can produce pro-angiogenic mediators and promote angiogenesis (18); and 4) fibrocytes are potent antigen presenting cells that can recruit and activate T cells (8).

In the context of a mouse model of bleomycin-induced pulmonary fibrosis, fibrocytes have been shown to home to the lungs and contribute to fibrosis (9). Human fibrocytes that were administered intravenously to severe combined immunodeficiency (SCID) mice, previously treated with either bleomycin or saline, preferentially homed to the lungs in animals treated with bleomycin. Similarly, in immunocompetent bleomycin-treated mice, the magnitude of lung pro-collagen I and III upregulation correlated with the number of CD45+ collagen I+ CXCR4+ fibrocytes in the bone marrow, blood and lung (9). Moreover, CXCL12 was significantly increased in the lungs of mice that were treated with bleomycin, supporting the notion that a CXCL12 gradient between the lungs and the plasma promoted the recruitment of the CD45+ collagen I+ CXCR4+ fibrocytes to the fibrotic lung. The administration of neutralising anti-CXCL12 antibodies to bleomycin-treated mice resulted in significantly reduced fibrocyte extravasation into the lung, reduced collagen deposition in the lungs, and reduced immunohistochemical expression of α-smooth muscle actin, but did not affect the numbers of other leukocyte populations in the lungs (9). Several groups have since corroborated these findings in the context of mouse models of lung fibrosis: bone marrow-derived mesenchymal stem cells home to the lung in response to injury, develop an epithelium-like phenotype, and reduce inflammation and collagen deposition (41, 42). Moreover, others have shown in a pulmonary irradiation model that fibrosis increases with fibrocyte recruitment to the lung (43); and that collagen-producing lung fibroblasts in pulmonary fibrosis caused by endotracheal bleomycin injection can also be derived from bone marrow-derived progenitor cells (44).

In a different murine model of lung fibrosis following intrapulmonary fluorescein isothiocyanate (FITC) administration, fibrocytes isolated from the bronchoalveolar lavage fluid and whole lung samples were found to express CCR2, CCR5, CCR7, as well as CXCR4 (38): the fibrocytes isolated from the lung expressed CCR2, migrated toward CCL2 and CCL12 ligands, and lost expression of CCR2 when cultured *in vitro* to a differentiated

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fibroblast. In CCR2-deficient mice challenged with intrapulmonary FITC, fibrocyte recruitment to the lungs was reduced. Moreover, wild-type mice that received CCR2 -/- bone marrow had reduced recruitment of fibrocytes to the lung and a reduction in pulmonary fibrosis. Transplantation of bone marrow cells from the wild-type mice into irradiated CCR2 -/- mice once again restored the ability to grow fibrocytes from whole lung homogenates and the susceptibility to FITC-induced lung fibrosis (38).

Additional data from the same investigators suggest that CCR2 ligands play a key role in the accumulation of fibrocytes triggered by intrapulmonary administration of FITC (51), and may be involved in the accumulation of fibrocytes in human diseases since the recruitment of human fibrocyte precursors (CD14+ CD16– monocytes) into areas of inflammation is dependent on CCR2 (32). The chemokine receptors CCR2 and CCR7 have also been shown to have important roles in the recruitment of fibrocytes in a model of renal fibrosis (52).

Lastly, data from several human studies suggest fibrocytes play a pivotal role in the pathogenesis of lung fibrosis. In one study, the numbers of CD45+, collagen I+, CXCR4+ circulating fibrocytes were markedly higher in patients with fibrotic interstitial lung disease than in healthy controls (11); the CXCL12 ligand expression was also found to be markedly elevated in the lung and plasma of patients with lung fibrosis. In another study, fibrocytes were identified in tissue from eight out of nine fibrotic lungs in patients with idiopathic pulmonary fibrosis. While there was a positive correlation between the abundance of fibroblastic foci and the amount of lung fibrocytes ($r=0.79$; $p<0.02$), no fibrocytes were identified in normal lungs (40). Moreover, CXCL12 was increased in the plasma of the patients with idiopathic pulmonary fibrosis (and present in about half of their bronchoalveolar samples); and the chemokine level directly correlated with disease severity (higher CXCL12 levels were associated with worse gas exchange) (40).

Fibrosis and aberrant airway remodelling in asthma

Repetitive episodes of airway inflammation and aberrant remodelling are the basis for the pathologic findings in these disorders: bronchial mucosa of asthmatic patients shows mixed degrees of both on-going inflammation and repair resulting in thickened walls. In one study, following inhalation of allergen, fibrocytes expressing CD34 and pro-collagen I mRNA were found in the airways of patients and a substantial proportion of these fibrocytes also expressed α-smooth muscle actin (29). Others have shown that in bronchial biopsies from patients with mild asthma, cells expressing CD34, CD45 and α-smooth muscle actin consistent with fibrocytes, differentiated into myofibroblasts and resulted in increased thickness of the lamina reticularis (53). The expression of CCR7 in the myofibroblasts in the bronchial mucosa in asthma patients in another study provides further evidence that these cells may be of fibrocyte origin (54). Moreover, these investigators also observed increased production of CCL19 and its receptor CCR7, suggesting that the CCL19/CCR7 axis may be important in fibrocyte recruitment in asthma (54). Lastly, it has been shown that in asthmatic patients with chronic airflow obstruction circulating fibrocytes are increased, and are transformed by TGF-β to myofibroblasts (55).

Fibrosis of the heart and vasculature

Intimal hyperplasia, the thickening of the tunica intima of blood vessels, is a universal response to vessel injury, and is an important cause of bypass graft failure and arterial restenosis following percutaneous revascularisation of coronary and peripheral arteries. In an ovine model of carotid artery intimal hyperplasia, a population of labeled circulating leukocytes that infiltrated the intima *in vivo* expressed CD45, CD34 and vimentin, and showed α-smooth muscle actin immunoreactivity during the remodelling process (15). Since this unique combination of surface markers is consistent with the surface markers of fibrocytes, the investigators suggested that intimal hyperplasia is, at least in part, caused by the migration of these cells (15).

In a rabbit model of atherosclerosis, compared to controls, the atherosclerotic plaque in rabbits fed a high cholesterol diet contained cells that stained positive for CD34, CD45, α-smooth muscle actin, and prolyl-4 hydroxylase on immunohistochemistry, suggesting a haematopoietic origin and fibroblast/myofibroblast-like phenotype (17). The fibrous cap plays an integral role in the stability of the atherosclerotic plaque: plaques with thin fibrous caps are more vulnerable to disruption and thrombotic vessel occlusion than those with thick fibrous caps. Recently, fibrocytes have been identified within the fibrous cap of human carotid endarterectomy specimens (16). These investigators examined atherosclerotic specimens for fibrocytes by immunohistochemistry staining for CD34, procollagen I and leukocyte-specific protein-1/procollagen I, and found fibrocytes in areas of plaque growth and tissue repair, suggesting that fibrocytes contribute to the formation and strength of the fibrous cap. Moreover, they found that these cells co-localized with TGF-β (known to promote fibrocyte formation).

In a closed chest mouse model of ischaemic cardiomyopathy, repetitive ischaemia/reperfusion episodes (consisting of multiple, daily 15-minute vessel occlusions, not associated with myocardial necrosis) resulted in a fibrotic cardiomyopathy, and global left ventricular dysfunction (56). The same investigators subsequently showed that these repetitive ischaemia/reperfusion episodes were associated with a markedly prolonged induction of CCL2; and that the resulting left ventricular dysfunction could be prevented by either genetic deletion of CCL2, or injection of a neutralizing anti-CCL2 antibody (57). In a separate study using the same model of ischaemic cardiomyopathy, in addition to prolonged induction of CCL2, increased numbers of small spindle-shaped cells in the myocardium that expressed collagen I, α-smooth muscle actin, CD34, and CD45, consistent with fibrocytes, were seen (45). Inhibition of circulating monocyte differentiation with serum amyloid P, a member of the pentraxin family of autocoids that binds to FcγR and modifies the phenotype and pathophysiological functions of monocytes (58), resulted in reduced fibrosis and improved global and regional ventricular function. Moreover, after treatment with serum amyloid P, isolated fibroblasts lacked the small spindle-shaped morphology characteristic of fibrocytes, and were identical to fibroblasts isolated from sham hearts; the subpopulation of CD34+/CD45+ cells were no longer detected (45). The haematopoietic origin of the fibrocyte was confirmed by using a chimeric mouse that expressed β-galactosidase in bone-marrow originating cells (45): after ischaemia/reperfusion a subpopulation of isolated cardiac

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fibroblasts demonstrated the distinctive morphology of fibrocytes (small spindle-shaped cells), and was positive for lacZ expression, as well as CD34 and collagen I.

Conclusion

The fibrocyte, a recently described and unique mesenchymal progenitor cell, exhibits characteristics of monocytes, fibroblasts and haematopoietic stem cells. Fibrocytes have been detected is a diverse group of fibrosing disorders effecting many organ systems including the lung, heart and the vasculature. Increasing evidence points to a pivotal role of these cells as an important source of fibroblasts and myofibroblasts during both physiologic and pathologic remodelling and repair processes. Additional data is needed from animal models and clinical studies to further elucidate these fibrotic mechanisms, and to ultimately translate the findings into novel therapeutic tools for selective manipulation of fibrosis in disease states.

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