Published in final edited form as:

Int J Biochem Cell Biol. 2010 April ; 42(4): 535–542. doi:10.1016/j.biocel.2009.10.014.

Fibrocytes: Bringing New Insights Into Mechanisms of Inflammation and Fibrosis

Ellen C. Keeley, M.D., M.S.^a, Borna Mehrad, M.D.^b, and Robert M. Strieter, M.D.^b

^aDepartment of Medicine, Division of Cardiology, University of Virginia, Charlottesville, Virginia

^bDepartment of Medicine, Division of Pulmonary and Critical Care Medicine, University of Virginia, Charlottesville, Virginia

Abstract

Regeneration and fibrosis are integral parts of the recovery process following tissue injury, and impaired regulation of these mechanisms is a hallmark of many chronic diseases. A population of bone marrow-derived mesenchymal progenitor cells known as fibrocytes, play an important role in tissue remodeling and fibrosis in both physiologic and pathologic settings. In this review we summarize the key concepts regarding the pathophysiology of wound healing and fibrosis, and present data to support the contention that circulating fibrocytes are important in both normal repair process and aberrant healing and fibrotic damage associated with a diverse set of disease states.

Keywords

Fibrocyte; Fibrosis

Introduction

Although the etiology of tissue damage may vary, the reparative process that ensues is remarkably similar (Kisseleva and Brenner, 2008a). Fibrosis is the end result of a series of events that occur after mechanical damage to the epithelium and/or endothelium (Kisseleva and Brenner, 2008b). Initially, inflammatory mediators are released that trigger platelet aggregation, clot formation and the formation of a provisional extracellular matrix. Subsequently, growth factors, cytokines and chemokines are produced and stimulate the proliferation and recruitment of leukocytes that work to remove dead tissue and promote new blood vessel formation. Activated fibroblasts transform into α -smooth muscle actin-expressing myofibroblasts that promote wound contraction. Lastly, epithelial and/or endothelial cells divide and migrate to regenerate the damaged tissue (Wynn, 2008). If this process becomes dysregulated, an excessive accumulation of extracellular matrix components occurs, and the synthesis of new collagen by fibroblasts exceeds the rate at which it is degraded. Over time fibrosis ensues which leads to permanent scarring and organ dysfunction (Kisseleva and Brenner, 2008b, Wynn, 2008).

© 2009 Elsevier Ltd. All rights reserved.

Correspondence to: Robert M. Strieter, MD, University of Virginia, Department of Medicine, Division of Pulmonary Critical Care, Box 800466, Charlottesville, Virginia 22908-0466, Tel. 434-982-6999, Fax. 434-243-0399, Strieter@Virginia.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

In the context of physiologic and pathologic fibrosis, tissue fibroblasts and myofibroblasts are classically thought to derive from *resident* fibroblasts that, in response to tissue injury, proliferate and express constituents of the extracellular matrix. However, it is now thought that fibroblasts can also be derived from two additional sources: (1) from epithelial cells, in a process known as epithelial-mesenchymal transition (Iwano et al., 2002, Kalluri and Neilson, 2003), and (2) from bone marrow-derived circulating progenitor cells (fibrocytes), the focus of this review (Abe et al., 2001, Bucala et al., 1994, Metz, 2003).

Fibrocytes

Original description

Fibrocytes were originally described in 1994 (Bucala et al., 1994): in an experimental model of wound repair, 10% of the cells in the wound chamber were spindle-shaped and expressed collagen, procollagen, and CD34 within one day following injury. Since their appearance was much faster than would be expected by entry of fibroblasts from the surrounding skin, it was thought that they must have originated from the circulation (Bucala, 2008). These cells were named fibrocytes (a term combining fibroblast with leukocyte). Fibrocytes are a unique CD45⁺ cell population that are distinct from monocytes, dendritic cells, T lymphocytes, fibroblasts, epithelial cells, endothelial cells, and Langerhans cells. They exhibit prominent cell surface projections on scanning electron microscopy making them morphologically distinct from leukocytes (Bucala et al., 1994). Fibrocytes comprise 0.1–1% of the nucleated cells in the peripheral blood in healthy hosts (Metz, 2003, Phillips et al., 2004, Quan et al., 2004).

Bone marrow origin

There is substantial information available supporting the hypothesis that fibrocytes are derived from the bone marrow. Fibrocytes are characterized by the expression of collagen I, collagen III, fibronectin, major histocompatibility complex II, CD11b, CD13, CD34, and CD45 but they do not express CD14, CD3, or CD10 (Abe et al., 2001, Aiba and Tagami, 1997, Bucala et al., 1994, Ebihara et al., 2006, Phillips et al., 2004, Pilling et al., 2003, Pilling et al., 2006, Quan et al., 2004, Yang et al., 2002). The co-expression of collagen and the other hematologic markers (such as CD45) are used to identify fibrocytes: early in culture, fibrocytes express CD34, CD45, collagen I, and vimentin. Fibrocytes also express a number of chemokine receptors on their surface including CCR3, CCR5, CCR7, and CXCR4, and can migrate to wound sites in response to specific chemokine gradients (Abe et al., 2001). They do not, however, express T cell markers (CD3, CD4, and CD8), B cell markers (CD19), the interleukin (IL)-2 receptor chain CD25, the low affinity Fc gamma receptor III (CD16), and myeloid markers (CD14 and nonspecific esterase) (Abe et al., 2001, Bucala et al., 1994, Metz, 2003, Phillips et al., 2004, Quan et al., 2004, Schmidt et al., 2003).

Some studies suggest that fibrocytes can differentiate from CD14⁺ peripheral blood monocytes that express the receptors for the Fc portion of IgG, CD64, and CD32 (Pilling et al., 2003, Pilling et al., 2006, Varcoe et al., 2006, Yang et al., 2002). Circulating fibrocytes may be present in a subset of CD14⁺ CD16[−] monocytes that carry the chemokine receptor, CCR2, on their surface (Gordon and Taylor, 2005, Tacke and Randolph, 2006). 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 (Gordon and Taylor, 2005, Tacke and Randolph, 2006). Human fibrocytes may represent an intermediate stage of differentiation of this monocyte subset into mature fibroblasts and myofibroblasts in tissue (Bellini and Mattoli, 2007). While fibrocytes are most likely of myeloid lineage, more information is needed to determine whether they are derived from a CD14⁺ progenitor cell.

Differentiation and trafficking

The differentiation of fibrocytes into myofibroblasts is augmented in the presence of transforming growth factor (TGF)- β or endothelin-1, and results in cells that produce fibronectin and collagen, and express the myofibroblast marker α -smooth muscle actin (Abe et al., 2001, Metz, 2003, Phillips et al., 2004, Quan et al., 2004, Schmidt et al., 2003). Fibrocytes spontaneously gain expression of α -smooth muscle actin in culture, and gradually lose the expression of CD34 and CD45 over time depending on the inflammatory milieu (Bucala, 2008): this response can be augmented by exposure of the fibrocytes to TGF- β or endothelin, resulting in differentiation into myofibroblast-type cells. 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 (Shao et al., 2008): 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. Fibrocyte differentiation appears to be influenced by a complex profile of cytokines, chemokines and plasma proteins within the area of tissue injury.

Human fibrocytes express several chemokine receptors, including CCR3, CCR5, CCR7, and CXCR4; in contrast, mouse fibrocytes express CXCR4, CCR7, and CCR2 (Abe et al., 2001, Phillips et al., 2004, Mehrad et al., 2009, Moore et al., 2005, Quan et al., 2004). Thus, in interpreting animal studies, it is important to note that the pattern of chemokine receptor expression is not identical between mouse and human fibrocytes. According to the disease process and organ involved, fibrocytes can use different chemokine ligand-receptor pairs for tissue homing. The CXCR4-CXCL12 axis plays an important role in the homing of bone marrow-derived progenitor cells (Murdoch, 2000): 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 (Abe et al., 2001), our group detected substantial *in vitro* and *in vivo* chemotaxis of these cells to CXCL12 (Phillips et al., 2004), and consider the earlier results to be due to methodological differences between the experiments, especially since hypoxia plays an important role for CXCR4 expression and chemotaxis (Mehrad et al., 2009).

Wound healing

Fibrocytes contribute to normal wound healing by several important mechanisms including acting as antigen-presenting cells (Chesney et al., 1997), serving as the contractile force of wound closure via α -smooth muscle actin expression (Abe et al., 2001, Metz, 2003), promoting angiogenesis (Hartlapp et al., 2001), producing cytokines, chemokines, and growth factors that induce fibroblast hyperplasia (Chesney et al., 1998), and secreting components of extracellular matrix (Abe et al., 2001, Bucala et al., 1994). Fibrocytes have been implicated in a wide range of aberrant fibrotic processes involving the lung, heart, and vasculature (Keeley et al., 2009), as well as the skin, kidney, bladder, liver, gallbladder, colon, pancreas, eye, and in infectious disease and tumor metastases.

Fibrotic diseases

Lung

Several lines of evidence support a role for fibrocytes in the development of lung fibrosis (Gomperts and Strieter, 2007). Fibrotic lung diseases are a large group of disorders characterized by varying degrees of inflammation and fibrosis of the lung parenchyma (2002). The clinical course is one of progressive replacement of lung tissue with scar tissue, and clinical deterioration. Among fibrotic lung diseases idiopathic pulmonary fibrosis is the most common.

Idiopathic pulmonary fibrosis—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 (Phillips et al., 2004). In this study, human fibrocytes that were administered intravenously to 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, in the blood, and in the lung (Phillips et al., 2004). In addition, 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 lung. The administration of neutralizing 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 (Phillips et al., 2004).

Several groups have since corroborated these findings in the context of mouse models of lung fibrosis (Ortiz et al., 2003, Rojas et al., 2005). Similar findings have been reported by other investigators using different models of lung fibrosis: (1) in a model of radiation-induced fibrosis, the degree of fibrosis correlated with fibrocyte recruitment to the lung (Epperly et al., 2003); (2) in an endotracheal bleomycin injection model, collagen-producing lung fibroblasts were shown to be derived from bone marrow progenitor cells (Hashimoto et al., 2004); and (3) in an intrapulmonary fluorescein isothiocyanate (FITC)-induced fibrosis model, fibrocytes isolated from the bronchoalveolar lavage fluid and whole lung samples were found to express CCR2, CCR5, CCR7, and CXCR4 (Moore et al., 2005). In the latter study, 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 fibroblast. In CCR2-deficient mice challenged with intrapulmonary FITC, fibrocyte recruitment to the lungs was reduced. Moreover, wildtype 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 wildtype 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 (Moore et al., 2005). Additional work from the same investigators suggest that CCR2 ligands play a key role in the accumulation of fibrocytes triggered by intrapulmonary administration of FITC (Moore et al., 2006), 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 (Tacke and Randolph, 2006).

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 (Mehrad et al., 2007); 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 8 out of 9 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 (Andersson-Sjoland et al., 2008). 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) (Andersson-Sjoland et al., 2008). In another study, the proportion of peripheral blood fibrocytes was shown to be increased in patients with acute exacerbations of interstitial pulmonary fibrosis as

compared to stable interstitial pulmonary fibrosis, and was an independent predictor of death (Moeller et al., 2009).

Asthma—Chronic asthma is characterized by persistent airway inflammation and structural aberrant remodeling of the airways (Davies et al., 2003). The bronchial mucosa of asthmatic patients shows mixed degrees of both on-going inflammation and repair. The remodeling process leads to thickening of the airway wall and can lead to irreversible decline in lung function. The subepithelial fibrosis in asthma is a result of extensive deposition of extracellular matrix and connective tissue components. 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 (Schmidt et al., 2003). Similarly, in a different study, a rapid increase in myofibroblasts was seen in the airway mucosa after allergen challenge in subjects with mild asthma (Gizycki et al., 1997). 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 (Nihlberg et al., 2006). These fibrocytes appeared in clusters close the epithelial basement membrane and their density correlated with the thickness of the lamina reticularis. The expression of CCR7 in the myofibroblasts in the bronchial mucosa in asthma patients was shown in another study and provides further evidence that these cells may be of fibrocyte origin (Kaur et al., 2006). These investigators also observed an increased production of CCL19 and its receptor CCR7, suggesting that the CCL19/CCR7 axis may be important in fibrocyte recruitment in asthma (Kaur et al., 2006).

Increased number of circulating fibrocytes has also been shown in patients with asthma. In one study, an increased number of CD34+ CD45+ Col I+ fibrocytes were found in the peripheral blood of patients with chronic persistent obstructive asthma, but not in patients with normal lung function (Wang et al., 2008). These fibrocytes had higher proliferation potential and increased differentiability into α -smooth muscle actin myofibroblasts when exposed to TGF- β 1. Moreover, there was a significant correlation between the percentage of fibrocytes in the peripheral blood of patients with chronic obstructive asthma and the average slope of the yearly decline in FEV1 (Wang et al., 2008). In a separate study, investigators found increased numbers of fibrocytes in the peripheral blood of patients with severe refractory asthma compared to normal controls ($1.4 \times 10^4/\text{mL}$ versus $0.4 \times 10^4/\text{mL}$, $p=0.002$). Moreover, they also found increased numbers of fibrocytes in the lamina propria from bronchial biopsy specimens in patients with severe refractory asthma compared to normal controls ($1.9/\text{mm}^2$ versus $0/\text{mm}^2$, $p<0.0001$) (Saunders et al., 2009). Lastly, since fibrocytes are potent antigen-presenting cells, they may amplify the allergic reaction by capturing antigens that cross the epithelial barrier (Chesney et al., 1997).

Pulmonary hypertension—Pulmonary hypertension is characterized by elevated pulmonary arterial pressures, increased pulmonary vascular resistance, and right ventricular failure (McLaughlin et al., 2009). The vascular remodeling seen in pulmonary hypertension is characterized by marked fibroproliferative changes in the pulmonary artery adventitia (Farber and Loscalzo, 2004). In a set of experiments using two different animal models of pulmonary hypertension (rats and calves), investigators showed a significant accumulation of fibrocytes in the adventitia and media of the remodeled pulmonary arteries (Frid et al., 2006). Moreover, the contribution of circulating fibrocytes to the vascular remodeling process was confirmed using depletion studies: reduction of fibrocytes in the circulation of chronically hypoxic rats led to a marked attenuation of adventitial thickening and decreased fibrosis (Frid et al., 2006). Others have also suggested a role for circulating bone marrow-derived cells in chronic hypoxia-induced remodeling. These investigators transplanted the bone marrow of enhanced green fluorescent protein (GFP)-transgenic mice to lethally irradiated syngeneic mice, and

exposed the chimera mice to hypoxia. Marked vascular remodeling was observed and a large number of GFP+ cells were observed in the adventitia of the pulmonary artery in the mice exposed to hypoxia compared to controls. These cells expressed α -smooth muscle actin and contributed to the pulmonary vascular remodeling process (Hayashida et al., 2005).

Urinary tract

Regardless of the specific etiology, renal fibrosis characterized by glomerulosclerosis and interstitial fibrosis, is the most common final pathway of renal failure (Sakai et al., 2006). Moreover, the extent of renal fibrosis within the kidney is an independent predictor of clinical outcomes (Nath, 1998). Histologically, renal fibrosis is defined by tubular atrophy and dilation, interstitial leukocyte infiltration, and increased interstitial matrix deposition. It has been estimated that up to 15% of the myofibroblasts contributing to renal fibrosis are of bone marrow origin (Kisseleva and Brenner, 2008a). The renin-angiotensin system and angiotensin II play significant roles in renal fibrosis: the renin-angiotensin system promotes inflammation by increased expression of cytokines, chemokines, growth factors, and reactive oxygen species, while angiotensin II induces endothelial dysfunction, and up-regulates adhesion molecules (Ruiz-Ortega et al., 2006). Moreover, in a murine model of renal fibrosis, it has been suggested that fibrocytes might contribute to fibrosis by an angiotensin II dependent pathway (Sakai et al., 2008). In this study, using two models of renal fibrosis (unilateral ureteral obstruction and chronic angiotensin II infusion) angiotensin II type 2 receptor-deficient mice had increased renal fibrosis and fibrocyte infiltration and a concomitant upregulation of procollagen type I compared with wild-type mice. In addition, the number of fibrocytes in the bone marrow of the angiotensin II type 2 receptor-deficient mice were increased. Pharmacologic inhibition of angiotensin II type 1 receptor reduced the degree of renal fibrosis and the number of fibrocytes in the kidney and in the bone marrow.

These same investigators examined whether the contribution of fibrocytes to renal fibrosis was dependent on their trafficking to the kidney via CCL21/CCR7 signaling (Sakai et al., 2006). In a murine model of renal fibrosis, they found that circulating CD45+ Col I+ fibrocytes infiltrated the diseased kidneys, and that these fibrocytes expressed CCR7. The inhibition of the CCL21/CCR7 signaling using a neutralizing antibody reduced the severity of the fibrocyte infiltration, the degree of kidney fibrosis (by almost 50%), and the renal expression of TGF- β 1 and Col I; thus suggesting that fibrocytes contribute to renal fibrosis by the production of Col I and that this process requires CCL21/CCR7 signaling. Moreover, CD34+ spindle shaped cells have also been detected in tubulointerstitial lesions in patients with glomerulonephritis and closely correlated with interstitial volume (Okon et al., 2003).

Lastly, in a pathologic study of chronic cystitis and invasive urothelial carcinomas of the bladder, CD34+ fibrocytes were found in the lamina propria and tunica muscularis in specimens obtained from patients with chronic cystitis, while there was complete loss of CD34+ fibrocytes in specimens obtained from patients with invasive urothelial carcinoma (Nimphius et al., 2007).

Multi-organ fibrotic diseases

Nephrogenic systemic fibrosis

Nephrogenic systemic fibrosis is a disease that occurs in patients with renal insufficiency, especially those who are dialysis-dependent, and is strongly associated with the use of gadolinium-based contrast agents (Galan et al., 2006, Morcos and Thomsen, 2008): The onset of the disease varies from several days to several months following exposure to gadolinium-based contrast. It is a debilitating disease that is characterized by the development of discolored plaques on the skin of the extremities and trunk. Over time, contractures develop and complete

loss of range of motion can occur. Although initially thought to affect only the skin (hence, the original name was nephrogenic fibrosing dermopathy), involvement of the lungs, heart and liver can occur (Mendoza et al., 2006) and is associated with increased mortality (Cowper et al., 2008, Marckmann et al., 2008). Histologically, fibrocytes defined as CD34+ Col I+ procollagen I+ cells populate the lesions of nephrogenic systemic fibrosis (Cowper and Bucala, 2003). Many questions remain about the pathogenesis of this disorder, the role of gadolinium-based contrast agents, and whether it is a disease of aberrant fibrocyte activation, trafficking or function (Bucala, 2008). Lastly, continued research into the pathophysiology of nephrogenic systemic fibrosis may shed light on other systemic fibrosing disorders such as systemic sclerosis and scleroderma.

Scleroderma

Scleroderma is a connective tissue disease of unknown etiology that is characterized by small vessel vasculopathy and irreversible fibrosis affecting the skin and other organs (LeRoy et al., 1988). Adenosine and one of its receptors (the adenosine A_{2A} receptor) have been shown to play important roles in the development of diffuse dermal fibrosis following bleomycin treatment in a murine model of scleroderma (Chan et al., 2006). In a separate study using the same model, investigators stained skin samples from normal mice, bleomycin-treated wild type A_{2A} receptor knock-out mice, and A_{2A} antagonist-treated mice for procollagen $\alpha 2$ Type I and CD34 (fibrocytes) (Katebi et al., 2008): the investigators found more fibrocytes in the dermis of the bleomycin-treated mice compared to the normal mice, and the increase in fibrocyte number was abrogated by blockade of the adenosine A_{2A} receptor, suggesting that recruitment of fibrocytes into tissue plays an important role in scleroderma. While a small case-control study of 8 patients with limited scleroderma, showed no difference between cases and controls in the expression of circulating monocyte surface molecules associated with fibrocytes (Russo et al., 2007), the study had major limitations including a small sample size and the enrollment of patients with limited scleroderma only.

It has previously been shown that patients with scleroderma have low levels of serum and tissue amyloid P compared to healthy controls (Pilling et al., 2003), and that serum levels of amyloid P play a key role in fibrocyte differentiation. In a study using specimens from scleroderma patients, investigators found very few CD34+ cells in the affected areas of skin compared to healthy controls and patients with other collagen vascular diseases (Aiba et al., 1994): a finding that is consistent with the observation that CD34 expression, which is increased during the early active inflammatory phase of wound healing, is down-regulated over time (Aiba and Tagami, 1997, Yang et al., 2005).

Skin

Fibrocytes play an integral role in the delicate balance between normal repair of skin wounds and pathologic fibrosis by regulating the production of extracellular matrix components as well as extracellular matrix-modifying enzymes (Metz, 2003). During the healing process of extensive burn wounds if excess deposition of extracellular matrix occurs, two different forms of aberrant wound healing (keloid and hypertrophic scar formation) may result (Ehrlich et al., 1994).

Keloid formation and hypertrophic scars

While keloids and hypertrophic scars are morphologically different, they share one important feature: over time the expression of CD34 on the fibrocytes within these wounds decreases, whereas the expression of proline-4-hydroxylase (an enzyme involved in collagen synthesis) increases (Aiba and Tagami, 1997), a finding that has been documented by others (Abe et al., 2001, Phillips et al., 2004). Moreover, in burn patients the number of circulating fibrocytes is

significantly increased (up to 10% of peripheral blood mononuclear cells) compared to that of normal individuals (<0.5%) (Yang et al., 2002). In hypertrophic scars, spindle-shaped cells expressing leukocyte-specific protein-1 and pro-collagen I (fibrocytes) are abundant (Yang et al., 2005). In a separate experimental model of wound healing, investigators found that cells that expressed α -smooth muscle actin were significantly increased in the wound compared to normal skin: these cells also expressed CD45, and CD34 thus consistent with fibrocytes (Mori et al., 2005). Similar experiments in female mice that received a male bone marrow transplant following total body irradiation, the Y chromosome was identified in the nuclei of the fibrocytes isolated from the wound site, supporting the role of fibrocytes in wound healing and their bone marrow origin (Mori et al., 2005). Lastly, it has been suggested that the predominant role of fibrocytes in hypertrophic scarring secondary to burn injury may be to regulate the function of local fibroblasts (Wang et al., 2007).

Gastrointestinal

Fibrocytes have also been implicated in the fibrosis of the liver, gallbladder, and pancreas. Regardless of the etiology, chronic liver disease can eventually lead to the excess accumulation of type I collagen and fibrosis. In a murine model of bile duct ligation-induced liver fibrosis, investigators found bone marrow-derived collagen-expressing GFP+ cells in the liver of chimeric mice (Kisseleva et al., 2006). The majority of these bone marrow-derived cells co-expressed collagen-GFP+ and CD45+, suggesting that collagen-producing fibrocytes were recruited from the bone marrow to the damaged liver (Kisseleva et al., 2006): it has been estimated that bone marrow-derived fibrocytes comprise 4–6% of all collagen-producing cells in the liver (Kisseleva and Brenner, 2008a).

The presence and distribution of CD34+ fibrocytes have been analyzed in neoplastic and inflammatory lesions of both the pancreas (Barth et al., 2002a, Kuroda et al., 2004), and the bladder (Nimphius et al., 2007). In one pathologic study, the stroma of normal pancreatic tissue had very few, diffusely scattered CD34+ fibrocytes, while tissue from patients with chronic pancreatitis had not only an increased number of CD34+ fibrocytes, but also an increased number of α -smooth muscle actin myofibroblasts (Barth et al., 2002a): Tissue obtained from pancreatic ductal adenocarcinoma, however, was devoid of CD34+ fibrocytes. Similar findings were reported in a separate study, and these investigators suggested that the CD34+ fibrocytes may play a role in the regulation of tumor growth in the pancreas (Kuroda et al., 2004).

In a pathologic study of normal gallbladder and chronic cholecystitis, myofibroblasts were absent from the wall of the normal gallbladder, but CD34+ cells were found in the stroma (Kuroda et al., 2005): In chronic cholecystitis, however, CD34+ cells were either absent or very limited in number and location. Lastly, investigators using a murine dextran sodium sulfate (DSS) colitis model showed that compared to normal mucosa without inflammation, there was a significant accumulation of immature oval-shaped CD45+ Col I+ fibrocytes in the submucosal layer of the colon on day 7 following the oral administration of 3% DSS, and by day 14 they had differentiated into the classically described spindle-shaped fibrocytes (Uehara et al., 2009). They also showed that the accumulation of CD45+ Col I+ fibrocytes preceded the appearance of α -smooth muscle actin + myofibroblasts. Regarding the shape of the cells, the investigators hypothesized that the oval-shaped fibrocytes seen during the early phase of colitis may be functioning as antigen-presenting cells, and that their differentiation into spindle-shaped cells may play an important role in initiating the healing process.

Stromal remodeling and tumor metastases

Stromal remodeling precipitated by invasive carcinomas is characterized by a loss of CD34+ expression and a gain of α -smooth muscle actin expression resulting in a phenotype change from CD34+ fibrocytes to α -smooth muscle actin myofibroblasts (Barth and Westhoff,

2007). This process is similar for many different tumors and may play a role in local invasion as well as systemic dissemination. It is thought that in the face of decreased antigen presentation by CD34+ fibrocytes, the hosts' immune control directed against invasive carcinoma cells may become dysregulated. The disappearance of CD34+ fibrocytes and the appearance of α -smooth muscle actin myofibroblasts associated with the transformation into an invasive tumor have been associated with tumors of the breast (Barth et al., 2002b, Ebrahimsade et al., 2007, Ramaswamy et al., 2003), cervix (Barth et al., 2002c), oral cavity/larynx/pharynx (Barth et al., 2004, Kojc et al., 2005), malignant melanoma (Wessel et al., 2008), anus (Sakai and Matsukuma, 2002), and renal pelvis and ureter (Kuroda et al., 2006).

Infectious disease

Lyme disease

Fibrocytes have been implicated in the pathogenesis of Lyme disease (Grab et al., 1999, Grab et al., 2002). In one study (Grab et al., 1999), fibrocytes from Rhesus monkeys were isolated and characterized by flow cytometry. *Borrelia burgdorferi* were incubated with human or monkey fibrocyte cultures in vitro. The investigators found that *B. burgdorferi* bound to both human and monkey fibrocytes in vitro, suggesting that the interaction between *B. burgdorferi* and peripheral blood fibrocytes may contribute to the inflammatory arthritis that is associated with Lyme disease.

Eye

Proliferative vitreoretinopathy is characterized by the development of fibrocellular membranes on the retina and is the most common cause of failure of retinal reattachment surgery. In an experiment using 16 epiretinal membranes from 16 eyes undergoing vitreoretinal surgery for the treatment of retinal detachment complicated by proliferative vitreoretinopathy investigators showed that cells expressing α -smooth muscle actin were present on all membranes (Abu El-Asrar et al., 2008). Moreover, using immunohistochemical techniques, there were cells that co-expressed both CD34 and α -smooth muscle actin and CD45 and α -smooth muscle actin. The investigators also demonstrated that the presence of CCR7+ α -smooth muscle actin+ and CXCR4+ α -smooth muscle actin+ cells and demonstrated that CCL21 and CXCL12 proteins were localized in myofibroblasts.

Heart and vasculature

Intimal hyperplasia

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 revascularization 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 remodeling process (Varcoe et al., 2006). 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 (Varcoe et al., 2006).

Atherosclerosis

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 hematopoietic origin and fibroblast/myofibroblast-like phenotype (Zulli et al., 2005). 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 (Medbury et al., 2008). 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 .

Ischemic cardiomyopathy

In a closed chest mouse model of ischemic cardiomyopathy, repetitive ischemia/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 (Dewald et al., 2003). The same investigators subsequently showed that these repetitive ischemia/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 (Dewald et al., 2005). In a separate study using the same model of ischemic 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 (Haudek et al., 2006). Inhibition of circulating monocyte differentiation with serum amyloid P, a member of the pentraxin family of autocoids that binds to Fc γ R and modifies the phenotype and pathophysiological functions of monocytes (Mold et al., 2002), 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 (Haudek et al., 2006). The hematopoietic origin of the fibrocyte was confirmed by using a chimeric mouse that expressed β -galactosidase in bone-marrow originating cells (Haudek et al., 2006): after ischemia/reperfusion a subpopulation of isolated cardiac fibroblasts demonstrated the distinctive morphology of fibrocytes (small spindle-shaped cells), and was positive for lacZ expression, as well as CD34 and collagen I.

Myxomatous mitral valve degeneration

Fibrocytes have been associated with myxomatous mitral valve degeneration the most common cause of isolated mitral valve insufficiency. In one study, myxomatous mitral valves removed from patients with mitral regurgitation, stained positive for vimentin (a characteristic of myofibroblasts) (Rabkin et al., 2001). In a separate pathologic study, investigators found that CD34+ fibrocytes made up the majority of mitral valve stromal cells, suggesting that CD34+ fibrocytes are involved in the pathogenesis of myxomatous mitral valve degeneration (Barth et al., 2005).

Conclusion

The bone marrow-derived fibrocyte is a unique circulating cell that plays a crucial role in both normal and aberrant healing processes. They maintain a pivotal position in balancing between normal healing and excess fibrosis that can lead to organ damage and ultimate failure. Further research is needed in order to more fully understand their role in health and disease.

Abbreviations

IL interleukin

IFN	interferon
DSS	dextran sodium sulfate
FITZ	fluorescein isothiocyanate
TGF	transforming growth factor

References

- American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. This joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS board of directors, June 2001 and by the ERS Executive Committee, June 2001. *Am J Respir Crit Care Med* 2002;165:277–304. [PubMed: 11790668]
- Abe R, Donnelly SC, Peng T, Bucala R, Metz CN. Peripheral blood fibrocytes: differentiation pathway and migration to wound sites. *J Immunol* 2001;166:7556–7562. [PubMed: 11390511]
- Abu El-Asrar AM, Struyf S, Van Damme J, Geboes K. Circulating fibrocytes contribute to the myofibroblast population in proliferative vitreoretinopathy epiretinal membranes. *Br J Ophthalmol* 2008;92:699–704. [PubMed: 18441176]
- Aiba S, Tabata N, Ohtani H, Tagami H. CD34+ spindle-shaped cells selectively disappear from the skin lesion of scleroderma. *Arch Dermatol* 1994;130:593–597. [PubMed: 7513987]
- Aiba S, Tagami H. Inverse correlation between CD34 expression and proline-4-hydroxylase immunoreactivity on spindle cells noted in hypertrophic scars and keloids. *J Cutan Pathol* 1997;24:65–69. [PubMed: 9162737]
- Andersson-Sjoland A, de Alba CG, Nihlberg K, Becerril C, Ramirez R, Pardo A, Westergren-Thorsson G, Selman M. Fibrocytes are a potential source of lung fibroblasts in idiopathic pulmonary fibrosis. *Int J Biochem Cell Biol* 2008;40:2129–2140. [PubMed: 18374622]
- Barth PJ, Ebrahimsade S, Hellinger A, Moll R, Ramaswamy A. CD34+ fibrocytes in neoplastic and inflammatory pancreatic lesions. *Virchows Arch* 2002a;440:128–133. [PubMed: 11964041]
- Barth PJ, Ebrahimsade S, Ramaswamy A, Moll R. CD34+ fibrocytes in invasive ductal carcinoma, ductal carcinoma in situ, and benign breast lesions. *Virchows Arch* 2002b;440:298–303. [PubMed: 11889601]
- Barth PJ, Koster H, Moosdorf R. CD34+ fibrocytes in normal mitral valves and myxomatous mitral valve degeneration. *Pathol Res Pract* 2005;201:301–304. [PubMed: 15991836]
- Barth PJ, Ramaswamy A, Moll R. CD34(+) fibrocytes in normal cervical stroma, cervical intraepithelial neoplasia III, and invasive squamous cell carcinoma of the cervix uteri. *Virchows Arch* 2002c; 441:564–568. [PubMed: 12461613]
- Barth PJ, Schenck zu Schweinsberg T, Ramaswamy A, Moll R. CD34+ fibrocytes, alpha-smooth muscle antigen-positive myofibroblasts, and CD117 expression in the stroma of invasive squamous cell carcinomas of the oral cavity, pharynx, and larynx. *Virchows Arch* 2004;444:231–234. [PubMed: 14758552]
- Barth PJ, Westhoff CC. CD34+ fibrocytes: morphology, histogenesis and function. *Curr Stem Cell Res Ther* 2007;2:221–227. [PubMed: 18220905]
- Bellini A, Mattoli S. The role of the fibrocyte, a bone marrow-derived mesenchymal progenitor, in reactive and reparative fibroses. *Lab Invest* 2007;87:858–870. [PubMed: 17607298]
- Bucala R. Circulating fibrocytes: cellular basis for NSF. *J Am Coll Radiol* 2008;5:36–39. [PubMed: 18180007]
- Bucala R, Spiegel LA, Chesney J, Hogan M, Cerami A. Circulating fibrocytes define a new leukocyte subpopulation that mediates tissue repair. *Mol Med* 1994;1:71–81. [PubMed: 8790603]
- Chan ES, Fernandez P, Merchant AA, Montesinos MC, Trzaska S, Desai A, Tung CF, Khoa DN, Pillinger MH, Reiss AB, Tomic-Canic M, Chen JF, Schwarzschild MA, Cronstein BN. Adenosine A2A receptors in diffuse dermal fibrosis: pathogenic role in human dermal fibroblasts and in a murine model of scleroderma. *Arthritis Rheum* 2006;54:2632–2642. [PubMed: 16871530]

- Chesney J, Bacher M, Bender A, Bucala R. The peripheral blood fibrocyte is a potent antigen-presenting cell capable of priming naive T cells in situ. *Proc Natl Acad Sci U S A* 1997;94:6307–6312. [PubMed: 9177213]
- Chesney J, Metz C, Stavitsky AB, Bacher M, Bucala R. Regulated production of type I collagen and inflammatory cytokines by peripheral blood fibrocytes. *J Immunol* 1998;160:419–425. [PubMed: 9551999]
- Cowper SE, Bucala R. Nephrogenic fibrosing dermopathy: suspect identified, motive unclear. *Am J Dermatopathol* 2003;25:358. [PubMed: 12876500]
- Cowper SE, Rabach M, Girardi M. Clinical and histological findings in nephrogenic systemic fibrosis. *Eur J Radiol* 2008;66:191–199. [PubMed: 18325705]
- Davies DE, Wicks J, Powell RM, Puddicombe SM, Holgate ST. Airway remodeling in asthma: new insights. *J Allergy Clin Immunol* 2003;111:215–225. quiz 226. [PubMed: 12589337]
- Dewald O, Frangogiannis NG, Zoerlein M, Duerr GD, Klemm C, Knuefermann P, Taffet G, Michael LH, Crapo JD, Welz A, Entman ML. Development of murine ischemic cardiomyopathy is associated with a transient inflammatory reaction and depends on reactive oxygen species. *Proc Natl Acad Sci U S A* 2003;100:2700–2705. [PubMed: 12586861]
- Dewald O, Zymek P, Winkelmann K, Koerting A, Ren G, Abou-Khamis T, Michael LH, Rollins BJ, Entman ML, Frangogiannis NG. CCL2/Monocyte Chemoattractant Protein-1 regulates inflammatory responses critical to healing myocardial infarcts. *Circ Res* 2005;96:881–889. [PubMed: 15774854]
- Ebihara Y, Masuya M, Larue AC, Fleming PA, Visconti RP, Minamiguchi H, Drake CJ, Ogawa M. Hematopoietic origins of fibroblasts: II. In vitro studies of fibroblasts, CFU-F, and fibrocytes. *Exp Hematol* 2006;34:219–229. [PubMed: 16459190]
- Ebrahimsade S, Westhoff CC, Barth PJ. CD34+ fibrocytes are preserved in most invasive lobular carcinomas of the breast. *Pathol Res Pract* 2007;203:695–698. [PubMed: 17656039]
- Ehrlich HP, Desmouliere A, Diegelmann RF, Cohen IK, Compton CC, Garner WL, Kapanci Y, Gabbiani G. Morphological and immunochemical differences between keloid and hypertrophic scar. *Am J Pathol* 1994;145:105–113. [PubMed: 8030742]
- Epperly MW, Guo H, Gretton JE, Greenberger JS. Bone marrow origin of myofibroblasts in irradiation pulmonary fibrosis. *Am J Respir Cell Mol Biol* 2003;29:213–224. [PubMed: 12649121]
- Farber HW, Loscalzo J. Pulmonary arterial hypertension. *N Engl J Med* 2004;351:1655–1665. [PubMed: 15483284]
- Frid MG, Brunetti JA, Burke DL, Carpenter TC, Davie NJ, Reeves JT, Roedersheimer MT, van Rooijen N, Stenmark KR. Hypoxia-induced pulmonary vascular remodeling requires recruitment of circulating mesenchymal precursors of a monocyte/macrophage lineage. *Am J Pathol* 2006;168:659–669. [PubMed: 16436679]
- Galan A, Cowper SE, Bucala R. Nephrogenic systemic fibrosis (nephrogenic fibrosing dermopathy). *Curr Opin Rheumatol* 2006;18:614–617. [PubMed: 17053507]
- Gizycki MJ, Adelroth E, Rogers AV, O'Byrne PM, Jeffery PK. Myofibroblast involvement in the allergen-induced late response in mild atopic asthma. *Am J Respir Cell Mol Biol* 1997;16:664–673. [PubMed: 9191468]
- Gomperts BN, Strieter RM. Fibrocytes in lung disease. *J Leukoc Biol* 2007;82:449–456. [PubMed: 17550974]
- Gordon S, Taylor PR. Monocyte and macrophage heterogeneity. *Nat Rev Immunol* 2005;5:953–964. [PubMed: 16322748]
- Grab DJ, Lanners H, Martin LN, Chesney J, Cai C, Adkisson HD, Bucala R. Interaction of *Borrelia burgdorferi* with peripheral blood fibrocytes, antigen-presenting cells with the potential for connective tissue targeting. *Mol Med* 1999;5:46–54. [PubMed: 10072447]
- Grab DJ, Salim M, Chesney J, Bucala R, Lanners HN. A role for peripheral blood fibrocytes in Lyme disease? *Med Hypotheses* 2002;59:1–10. [PubMed: 12160674]
- Hartlapp I, Abe R, Saeed RW, Peng T, Voelter W, Bucala R, Metz CN. Fibrocytes induce an angiogenic phenotype in cultured endothelial cells and promote angiogenesis in vivo. *FASEB J* 2001;15:2215–2224. [PubMed: 11641248]
- Hashimoto N, Jin H, Liu T, Chensue SW, Phan SH. Bone marrow-derived progenitor cells in pulmonary fibrosis. *J Clin Invest* 2004;113:243–252. [PubMed: 14722616]

- Haudek SB, Xia Y, Huebener P, Lee JM, Carlson S, Crawford JR, Pilling D, Gomer RH, Trial J, Frangogiannis NG, Entman ML. Bone marrow-derived fibroblast precursors mediate ischemic cardiomyopathy in mice. *Proc Natl Acad Sci U S A* 2006;103:18284–18289. [PubMed: 17114286]
- Hayashida K, Fujita J, Miyake Y, Kawada H, Ando K, Ogawa S, Fukuda K. Bone marrow-derived cells contribute to pulmonary vascular remodeling in hypoxia-induced pulmonary hypertension. *Chest* 2005;127:1793–1798. [PubMed: 15888860]
- Iwano M, Plieth D, Danoff TM, Xue C, Okada H, Neilson EG. Evidence that fibroblasts derive from epithelium during tissue fibrosis. *J Clin Invest* 2002;110:341–350. [PubMed: 12163453]
- Kalluri R, Neilson EG. Epithelial-mesenchymal transition and its implications for fibrosis. *J Clin Invest* 2003;112:1776–1784. [PubMed: 14679171]
- Katebi M, Fernandez P, Chan ES, Cronstein BN. Adenosine A2A receptor blockade or deletion diminishes fibrocyte accumulation in the skin in a murine model of scleroderma, bleomycin-induced fibrosis. *Inflammation* 2008;31:299–303. [PubMed: 18709547]
- Kaur D, Saunders R, Berger P, Siddiqui S, Woodman L, Wardlaw A, Bradding P, Brightling CE. Airway smooth muscle and mast cell-derived CC chemokine ligand 19 mediate airway smooth muscle migration in asthma. *Am J Respir Crit Care Med* 2006;174:1179–1188. [PubMed: 16959919]
- Keeley EC, Mehrad B, Strieter RM. The role of circulating mesenchymal progenitor cells (fibrocytes) in the pathogenesis of fibrotic disorders. *Thromb Haemost* 2009;101:613–618. [PubMed: 19350102]
- Kisseleva T, Brenner DA. Fibrogenesis of parenchymal organs. *Proc Am Thorac Soc* 2008a;5:338–342. [PubMed: 18403330]
- Kisseleva T, Brenner DA. Mechanisms of fibrogenesis. *Exp Biol Med (Maywood)* 2008b;233:109–122. [PubMed: 18222966]
- Kisseleva T, Uchinami H, Feirt N, Quintana-Bustamante O, Segovia JC, Schwabe RF, Brenner DA. Bone marrow-derived fibrocytes participate in pathogenesis of liver fibrosis. *J Hepatol* 2006;45:429–438. [PubMed: 16846660]
- Kojc N, Zidar N, Vodopivec B, Gale N. Expression of CD34, alpha-smooth muscle actin, and transforming growth factor beta1 in squamous intraepithelial lesions and squamous cell carcinoma of the larynx and hypopharynx. *Hum Pathol* 2005;36:16–21. [PubMed: 15712177]
- Kuroda N, Guo L, Miyazaki E, Hamauzu T, Toi M, Hiroi M, Enzan H. The appearance of myofibroblasts and the disappearance of CD34-positive stromal cells in the area adjacent to xanthogranulomatous foci of chronic cholecystitis. *Histol Histopathol* 2005;20:127–133. [PubMed: 15578431]
- Kuroda N, Shimasaki N, Miyazaki E, Hamauzu T, Toi M, Hiroi M, Shuin T, Enzan H. The distribution of myofibroblasts and CD34-positive stromal cells in normal renal pelvis and ureter and their cancers. *Histol Histopathol* 2006;21:1303–1307. [PubMed: 16977581]
- Kuroda N, Toi M, Nakayama H, Miyazaki E, Yamamoto M, Hayashi Y, Hiroi M, Enzan H. The distribution and role of myofibroblasts and CD34-positive stromal cells in normal pancreas and various pancreatic lesions. *Histol Histopathol* 2004;19:59–67. [PubMed: 14702172]
- LeRoy EC, Black C, Fleischmajer R, Jablonska S, Krieg T, Medsger TA Jr, Rowell N, Wollheim F. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. *J Rheumatol* 1988;15:202–205. [PubMed: 3361530]
- Marckmann P, Skov L, Rossen K, Thomsen HS. Clinical manifestation of gadodiamide-related nephrogenic systemic fibrosis. *Clin Nephrol* 2008;69:161–168. [PubMed: 18397714]
- McLaughlin VV, Archer SL, Badesch DB, Barst RJ, Farber HW, Lindner JR, Mathier MA, McGoon MD, Park MH, Rosenson RS, Rubin LJ, Tapson VF, Varga J. ACCF/AHA 2009 expert consensus document on pulmonary hypertension a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc.; and the Pulmonary Hypertension Association. *J Am Coll Cardiol* 2009;53:1573–1619. [PubMed: 19389575]
- Medbury HJ, Tarran SL, Guiffre AK, Williams MM, Lam TH, Vicaretti M, Fletcher JP. Monocytes contribute to the atherosclerotic cap by transformation into fibrocytes. *Int Angiol* 2008;27:114–123. [PubMed: 18427397]
- Mehrad B, Burdick MD, Strieter RM. Fibrocyte CXCR4 regulation as a therapeutic target in pulmonary fibrosis. *Int J Biochem Cell Biol* 2009;41:1708–1718. [PubMed: 19433312]

- Mehrad B, Burdick MD, Zisman DA, Keane MP, Belperio JA, Strieter RM. Circulating peripheral blood fibrocytes in human fibrotic interstitial lung disease. *Biochem Biophys Res Commun* 2007;353:104–108. [PubMed: 17174272]
- Mendoza FA, Artlett CM, Sandorfi N, Latinis K, Piera-Velazquez S, Jimenez SA. Description of 12 cases of nephrogenic fibrosing dermopathy and review of the literature. *Semin Arthritis Rheum* 2006;35:238–249. [PubMed: 16461069]
- Metz CN. Fibrocytes: a unique cell population implicated in wound healing. *Cell Mol Life Sci* 2003;60:1342–1350. [PubMed: 12943223]
- Moeller A, Gilpin SE, Ask K, Cox G, Cook D, Gauldie J, Margetts PJ, Farkas L, Dobranowski J, Boylan C, O'Byrne PM, Strieter RM, Kolb M. Circulating fibrocytes are an indicator of poor prognosis in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2009;179:588–594. [PubMed: 19151190]
- Mold C, Baca R, Du Clos TW. Serum amyloid P component and C-reactive protein opsonize apoptotic cells for phagocytosis through Fcγ receptors. *J Autoimmun* 2002;19:147–154. [PubMed: 12419285]
- Moore BB, Kolodnick JE, Thannickal VJ, Cooke K, Moore TA, Hogaboam C, Wilke CA, Toews GB. CCR2-mediated recruitment of fibrocytes to the alveolar space after fibrotic injury. *Am J Pathol* 2005;166:675–684. [PubMed: 15743780]
- Moore BB, Murray L, Das A, Wilke CA, Herrygers AB, Toews GB. The role of CCL12 in the recruitment of fibrocytes and lung fibrosis. *Am J Respir Cell Mol Biol* 2006;35:175–181. [PubMed: 16543609]
- Morcos SK, Thomsen HS. Nephrogenic systemic fibrosis: more questions and some answers. *Nephron Clin Pract* 2008;110:c24–c31. discussion c32. [PubMed: 18688172]
- Mori L, Bellini A, Stacey MA, Schmidt M, Mattoli S. Fibrocytes contribute to the myofibroblast population in wounded skin and originate from the bone marrow. *Exp Cell Res* 2005;304:81–90. [PubMed: 15707576]
- Murdoch C. CXCR4: chemokine receptor extraordinaire. *Immunol Rev* 2000;177:175–184. [PubMed: 11138774]
- Nath KA. The tubulointerstitium in progressive renal disease. *Kidney Int* 1998;54:992–994. [PubMed: 9734628]
- Nihlberg K, Larsen K, Hultgardh-Nilsson A, Malmstrom A, Bjerner L, Westergren-Thorsson G. Tissue fibrocytes in patients with mild asthma: a possible link to thickness of reticular basement membrane? *Respir Res* 2006;7:50. [PubMed: 16571120]
- Nimphius W, Moll R, Olbert P, Ramaswamy A, Barth PJ. CD34+ fibrocytes in chronic cystitis and noninvasive and invasive urothelial carcinomas of the urinary bladder. *Virchows Arch* 2007;450:179–185. [PubMed: 17149610]
- Okon K, Szumera A, Kuzniewski M. Are CD34+ cells found in renal interstitial fibrosis? *Am J Nephrol* 2003;23:409–414. [PubMed: 14566107]
- Ortiz LA, Gambelli F, McBride C, Gaupp D, Baddoo M, Kaminski N, Phinney DG. Mesenchymal stem cell engraftment in lung is enhanced in response to bleomycin exposure and ameliorates its fibrotic effects. *Proc Natl Acad Sci U S A* 2003;100:8407–8411. [PubMed: 12815096]
- Phillips RJ, Burdick MD, Hong K, Lutz MA, Murray LA, Xue YY, Belperio JA, Keane MP, Strieter RM. Circulating fibrocytes traffic to the lungs in response to CXCL12 and mediate fibrosis. *J Clin Invest* 2004;114:438–446. [PubMed: 15286810]
- Pilling D, Buckley CD, Salmon M, Gomer RH. Inhibition of fibrocyte differentiation by serum amyloid P. *J Immunol* 2003;171:5537–5546. [PubMed: 14607961]
- Pilling D, Tucker NM, Gomer RH. Aggregated IgG inhibits the differentiation of human fibrocytes. *J Leukoc Biol* 2006;79:1242–1251. [PubMed: 16543402]
- Quan TE, Cowper S, Wu SP, Bockenstedt LK, Bucala R. Circulating fibrocytes: collagen-secreting cells of the peripheral blood. *Int J Biochem Cell Biol* 2004;36:598–606. [PubMed: 15010326]
- Rabkin E, Aikawa M, Stone JR, Fukumoto Y, Libby P, Schoen FJ. Activated interstitial myofibroblasts express catabolic enzymes and mediate matrix remodeling in myxomatous heart valves. *Circulation* 2001;104:2525–2532. [PubMed: 11714645]
- Ramaswamy A, Moll R, Barth PJ. CD34+ fibrocytes in tubular carcinomas and radial scars of the breast. *Virchows Arch* 2003;443:536–540. [PubMed: 12898244]

- Rojas M, Xu J, Woods CR, Mora AL, Spears W, Roman J, Brigham KL. Bone marrow-derived mesenchymal stem cells in repair of the injured lung. *Am J Respir Cell Mol Biol* 2005;33:145–152. [PubMed: 15891110]
- Ruiz-Ortega M, Ruperez M, Esteban V, Rodriguez-Vita J, Sanchez-Lopez E, Carvajal G, Egido J. Angiotensin II: a key factor in the inflammatory and fibrotic response in kidney diseases. *Nephrol Dial Transplant* 2006;21:16–20. [PubMed: 16280370]
- Russo R, Medbury H, Guiffre A, Englert H, Manolios N. Lack of increased expression of cell surface markers for circulating fibrocyte progenitors in limited scleroderma. *Clin Rheumatol* 2007;26:1136–1141. [PubMed: 17061153]
- Sakai N, Wada T, Matsushima K, Bucala R, Iwai M, Horiuchi M, Kaneko S. The renin-angiotensin system contributes to renal fibrosis through regulation of fibrocytes. *J Hypertens* 2008;26:780–790. [PubMed: 18327089]
- Sakai N, Wada T, Yokoyama H, Lipp M, Ueha S, Matsushima K, Kaneko S. Secondary lymphoid tissue chemokine (SLC/CCL21)/CCR7 signaling regulates fibrocytes in renal fibrosis. *Proc Natl Acad Sci U S A* 2006;103:14098–14103. [PubMed: 16966615]
- Sakai Y, Matsukuma S. CD34+ stromal cells and hyalinized vascular changes in the anal fibroepithelial polyps. *Histopathology* 2002;41:230–235. [PubMed: 12207784]
- Saunders R, Siddiqui S, Kaur D, Doe C, Sutcliffe A, Hollins F, Bradding P, Wardlaw A, Brightling CE. Fibrocyte localization to the airway smooth muscle is a feature of asthma. *J Allergy Clin Immunol* 2009;123:376–384. [PubMed: 19081612]
- Schmidt M, Sun G, Stacey MA, Mori L, Mattoli S. Identification of circulating fibrocytes as precursors of bronchial myofibroblasts in asthma. *J Immunol* 2003;171:380–389. [PubMed: 12817021]
- Shao DD, Suresh R, Vakil V, Gomer RH, Pilling D. Pivotal Advance: Th-1 cytokines inhibit, and Th-2 cytokines promote fibrocyte differentiation. *J Leukoc Biol* 2008;83:1323–1333. [PubMed: 18332234]
- Tacke F, Randolph GJ. Migratory fate and differentiation of blood monocyte subsets. *Immunobiology* 2006;211:609–618. [PubMed: 16920499]
- Uehara H, Nakagawa T, Katsuno T, Sato T, Isono A, Noguchi Y, Saito Y. Emergence of Fibrocytes Showing Morphological Changes in the Inflamed Colonic Mucosa. *Dig Dis Sci*. 2009
- Varcoe RL, Mikhail M, Guiffre AK, Pennings G, Vicaretti M, Hawthorne WJ, Fletcher JP, Medbury HJ. The role of the fibrocyte in intimal hyperplasia. *J Thromb Haemost* 2006;4:1125–1133. [PubMed: 16689767]
- Wang CH, Huang CD, Lin HC, Lee KY, Lin SM, Liu CY, Huang KH, Ko YS, Chung KF, Kuo HP. Increased circulating fibrocytes in asthma with chronic airflow obstruction. *Am J Respir Crit Care Med* 2008;178:583–591. [PubMed: 18583572]
- Wang JF, Jiao H, Stewart TL, Shankowsky HA, Scott PG, Tredget EE. Fibrocytes from burn patients regulate the activities of fibroblasts. *Wound Repair Regen* 2007;15:113–121. [PubMed: 17244327]
- Wessel C, Westhoff CC, Nowak K, Moll I, Barth PJ. CD34(+) fibrocytes in melanocytic nevi and malignant melanomas of the skin. *Virchows Arch* 2008;453:485–489. [PubMed: 18813945]
- Wynn TA. Cellular and molecular mechanisms of fibrosis. *J Pathol* 2008;214:199–210. [PubMed: 18161745]
- Yang L, Scott PG, Dodd C, Medina A, Jiao H, Shankowsky HA, Ghahary A, Tredget EE. Identification of fibrocytes in postburn hypertrophic scar. *Wound Repair Regen* 2005;13:398–404. [PubMed: 16008729]
- Yang L, Scott PG, Giuffre J, Shankowsky HA, Ghahary A, Tredget EE. Peripheral blood fibrocytes from burn patients: identification and quantification of fibrocytes in adherent cells cultured from peripheral blood mononuclear cells. *Lab Invest* 2002;82:1183–1192. [PubMed: 12218079]
- Zulli A, Buxton BF, Black MJ, Hare DL. CD34 Class III positive cells are present in atherosclerotic plaques of the rabbit model of atherosclerosis. *Histochem Cell Biol* 2005;124:517–522. [PubMed: 16177890]