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REVIEW

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Fibrocytes and the tissue niche in lung repair

Annika Andersson-Sjöland^{1*}, Kristian Nihlberg¹, Leif Eriksson², Leif Bjermer² and Gunilla Westergren-Thorsson^{1,2}

Abstract

Human fibrocytes are bone marrow-derived mesenchymal progenitor cells that express a variety of markers related to leukocytes, hematopoietic stem cells and a diverse set of fibroblast phenotypes. Fibrocytes can be recruited from the circulation to the tissue where they further can differentiate and proliferate into various mesenchymal cell types depending on the tissue niche. This local tissue niche is important because it modulates the fibrocytes and coordinates their role in tissue behaviour and repair. However, plasticity of a niche may be co-opted in chronic airway diseases such as asthma, idiopathic pulmonary fibrosis and obliterative bronchiolitis. This review will therefore focus on a possible role of fibrocytes in pathological tissue repair processes in those diseases.

Introduction

Tissue repair and remodelling are ongoing processes in all types of wound healing. In healthy subjects, the primary role of the extracellular matrix (ECM) is to provide tissues with specific mechanical properties and to serve as a structural framework for cell attachment and migration. An ongoing tissue repair can result in fibrosis, which is regarded as an abnormal wound-healing process. Both resident tissue cells and recruited cells play significant roles in the pathological tissue repair.

Mesenchymal stem cells and progenitor cells have recently emerged as being important for maintaining tissue homeostasis. The dynamic relationship between the stem cells and the niche is very evident during tissue repair after an injury. Constitutive activation of repair programs, including accompanying inflammatory responses, leads to permanent changes in the niche that can lead to dysregulation of cellular function and stem cell behaviour. This can ultimately contribute to the disease progression, and therefore it is necessary to understand the molecular structure and composition of the niche to understand stem cell behaviour.

Fibrocytes - markers, recruitment, and differentiation

A few years ago tissue-resident fibroblasts were thought to be the only possible source of fibroblasts. However, fibrocytes have recently been discovered as one of several different precursors of fibroblasts [1]. Epithelial-

mesenchymal transition and endothelial-mesenchymal transition are also known to be possible sources of fibroblasts [2,3]. To evaluate the portion that each possible progenitor contributes to the fibroblast population, a bleomycin-induced model of lung fibrosis was studied. In this model, one-third of the fibroblasts were derived from epithelium and one-fifth from bone marrow. The proportions derived from endothelial-mesenchymal transition and from other possible origins were not investigated in this study [4]. Further studies are required to fully understand the mesenchymal origins of fibroblasts.

Fibrocytes are a distinct sub-population of bone marrow-derived fibroblast-like cells that can be found in the tissue and as circulating cells in peripheral blood. A combination of specific markers is used to identify fibrocytes such as combining haematopoietic markers with mesenchymal markers. For example, there are molecules specific for leukocytes (CD45), monocytes (CD11a, CD11b, CD13), and stem cells (CD34), and also chemokine receptors (CXCR4), major histocompatibility complex (MHC) molecules, and mesenchymal markers (prolyl 4-hydroxylase, α -smooth muscle actin (α -SMA)) on fibrocytes [1,5-8]. One of the most abundant markers is CXCR4, which is expressed by 90% of circulating fibrocytes [9]. The expression of these specific proteins alters as the fibrocytes are released from the bone marrow and recruited to the tissue. Mori *et al.* (10) isolated circulating fibrocytes from mice and analysed the cells regarding their CD13, CD34, CD45, collagen I, and α -SMA expression for one week in serum-free medium or in medium supplemented with transforming growth factor (TGF) β , a factor involved in wound healing. The

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expression of CD13, CD34, and CD45 decreased, whereas the expression of collagen I was constantly high, and the expression of α -SMA was increased. The differences were even higher when TGF- β was present [10].

In the tissue, fibrocytes can also play a role in angiogenesis. For example, *in vitro*, fibrocytes produce a number of pro-angiogenic factors such as basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF), granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin (IL)-1, IL-8, and macrophage colony-stimulating factor (M-CSF). These factors induce migration, proliferation, and alignment of endothelial cells into tube-like structures [11]. Fibrocytes express matrix metalloproteinases (MMP)-2, MMP-7, MMP-8, and MMP-9, which can degrade ECM molecules. Such proteinases can also alter the behavior of intra- and extracellular proteins and further regulate the fibrocytes' possibility for proliferation, adhesion, migration, and chemotaxis [12].

Fibrocytes have to be recruited from the bone marrow to the injured tissue, and one of the possibilities for recruitment is the CXCR4-stromal cell-derived factor (SDF)-1/CXCL12 axis. SDF-1/CXCL12 belongs to the CXC family. The only receptor for SDF-1/CXCL12 is the G-protein-coupled seven-span transmembrane receptor CXCR4 [13], which is present on its target cell, e.g., the fibrocyte. Binding to receptor causes several

changes to the fibrocyte: increased secretion of MMPs, VEGF, and nitric oxide (NO), as well as cytoskeletal rearrangements which give increased mobility and chemotaxis [14]. The surrounding ECM forms a micro-environment to which cells can attach, and the ECM forms the basement membrane located under the epithelial and endothelial cells. The main components of the ECM are collagens, proteoglycans, hyaluronan, and other glycoproteins. The ECM functions as a reservoir for growth factors and chemokines, and it is also a water-absorbent gel mass that gives the tissue its specific features. Under physiological conditions, the ECM turnover rate is highly controlled. Under pathological conditions, such as during tissue repair, there is a higher rate of synthesis and/or lower rate of degradation. The remodelling is closely associated with inflammatory processes, and some molecules involved in inflammation, such as hyaluronan, fibronectin, and fibrinogen, appear to increase the fibrocyte's sensitivity to SDF-1/CXCL12 [14,15] (Figure 1).

The importance of the CXCR4 - SDF-1/CXCL12 axis has been shown by Phillips *et al.* using a bleomycin model of lung fibrosis. Mice treated with anti-CXCL12 antibodies had significantly lower levels of collagen and α -SMA than mice treated with control antibodies [16]. Another possible mechanism for recruitment is a gradient of the chemokine secondary lymphoid tissue chemokine/chemokine ligand 21 (SLC/CCL21) [17]. It is

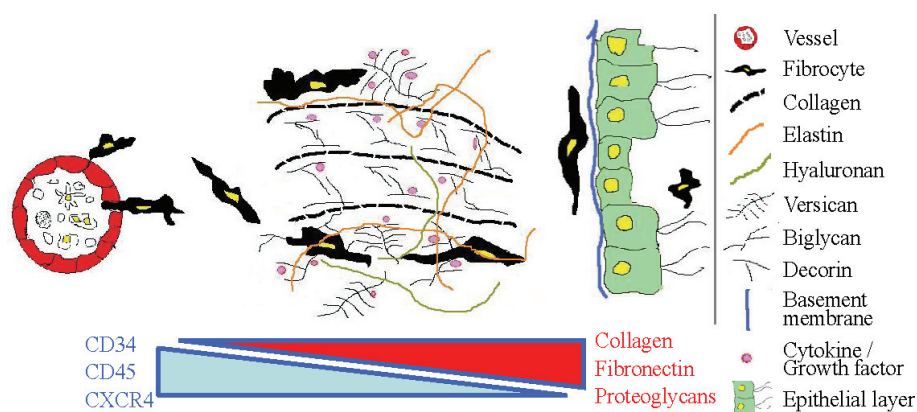


Figure 1 Dynamic/temporal local micro-environmental niche. The CXCR4-expressing fibrocytes are recruited from the circulation to the tissue by a gradient of stromal cell-derived factor (SDF)-1/CXCL12. In the tissue the fibrocytes move and interact with the dynamic/temporal local micro-environmental niche consisting of a broad array of extracellular matrix (ECM) molecules such as collagens, proteoglycans, hyaluronan, and glycoproteins. The ECM forms a network and acts as a supporting structure for tissue integrity. It is very essential that the ECM can also function as a reservoir for a large number of growth factors and cytokines, e.g., SDF-1/CXCL12, transforming growth factor (TGF)- β , interleukin (IL)-8, tumor necrosis factor (TNF)- α , platelet-derived growth factor (PDGF), and vascular endothelial growth factor (VEGF), just to mention some examples (generalized as violet spots in the figure) [55,56]. However, in disease states, the structure and composition of the ECM is changed, and that strongly affects the activity of cells in the niche. The alteration of the ECM, of course, is dependent on type of disease, state of disease, gene signature, age, gender, nutrition, infection, and also physical location in the pulmonary tree. It is important that the expression of the haematopoietic surface receptors, CD34, CD45, and CXCR4, on the fibrocytes gradually decreases, whereas the expression of the mesenchymal markers, such as collagen, fibronectin, and proteoglycans, gradually increases during the fibrocytes' journey through the tissue. The fibrocyte can also migrate to the lumen of the airway, and it has been detected there in both asthma and IPF.

normally expressed in lymphoid organs but is also found in lung tissue under inflammatory conditions. The receptor for SLC/CCL21 is CCR7, but it is only expressed by less than 10% of circulating fibrocytes [9]. This way of recruitment has been studied mostly in papers on renal fibrosis [5,18].

When fibrocytes have entered an injured tissue, they migrate through the tissue and are attracted to specific cytokines that are bound to the ECM. In disease-specific matrix (described below), the cytokine composition influences recruitment, differentiation and behaviour of fibrocytes, e.g., SDF-1 induces migration by interacting with CXCR4. The markers on the fibrocytes change during recruitment in the injured tissue. The expression of mesenchymal markers increases, while haematopoietic markers decrease [17] (Figure 1). In many ways fibrocytes differ from fibroblasts. An immunologically important difference is antigen presentation. Fibrocytes express both MHC class I and class II antigens and co-factors CD80 and CD86. Furthermore, fibrocytes can migrate to lymphatic organs and sensitise naive T-cells. Previously, this feature was only thought to be a task of dendritic cells [19].

Another possible goal for the differentiation of fibrocytes is to become adipocytes and chondrocytes. The differentiation to adipocytes is driven by specific adipogenic hormones and cytokines which follow activation of specific adipocyte genes. On the other hand, TGF- β inhibits this differentiation by activating stress-activated protein kinase/c-Jun NH2-terminal kinase mitogen activated protein kinase (SAPK/JNK MAPK), which is normally suppressed during differentiation to adipocytes [20]. Furthermore, the differentiation to chondrocytes is driven by TGF- β 3 together with a medium that differentiates mesenchymal stem cells to chondrocytes [21]. Interestingly, fibrocytes that have a chondrocyte-like

phenotype show an increased expression of aggrecan and collagen [21].

Tissue repair in lung disorders

Today, both fibrocytes and fibroblasts are known to be important in wound healing as ECM-producing cells that function in response to injury. We also know that they can release cytokines and growth factors that are central for remodelling. In the lung, fibrosis can occur at different locations – at the macro-level in the central part of the lung, at the micro-level in the distal alveolar parenchyma, and something in-between, in the small airways. In this review we have included three different patient groups, believed to differ somewhat in the primary site of fibrotic deposition. In asthma, the basement membrane, which is located below the epithelial layer, is thickened because of accumulation of collagens and proteoglycans [22] (Figure 2a). In idiopathic pulmonary fibrosis (IPF), fibroblastic foci occur in demarcated areas, which are rich in ECM and proteoglycans, but with few cells [23] (Figure 2b). In obliterative bronchiolitis (OB), the small airways are obliterated with ECM [24-26], where the proteoglycans function as “staples” to attach the connective tissue. In OB, the parenchymal part of the lung is also involved with thickening of the alveolar septa [27] (Figure 2c).

The above mentioned disorders are chronic diseases that involve remodelling of both the airways and the pulmonary vessels. The remodelling processes have many differences, but, surprisingly, also many similarities even though the underlying pathophysiological mechanisms are different. Remodelling usually starts with an epithelial injury that later gives rise to structural changes in the airways and in the lung. The origins of these disorders are different, but they have a common denominator – the ECM deposition changes the lung



Figure 2 Characteristic tissue niche in chronic airway diseases. Panel (a) shows a histological section from a patient with IPF, characterized by a fibroblastic foci (outlined area) located below the epithelial layer (arrows). The fibroblastic foci is an area rich in ECM but with only few cells with a stretched morphology, located in parallel to the alveolar septa cells. Panel (b) shows a histological section from a patient with asthma, characterized by thickening of the basement membrane (arrows), shedding of the epithelial layer (closed arrowheads) and formation of peribronchial fibrosis (open arrowheads). Panel (c) shows a partially obliterated bronchiole (outlined area) in a patient with OB after lung transplantation. OB is histologically identified as ECM plugs with few fibroblasts. Original magnification 20 $\times$. Scale bar = 100 μ m.

structure, causes deterioration of the tissue, and thereby decreased lung function.

Niche plasticity

Idiopathic Pulmonary Fibrosis

Many cell types are important in the pathology of IPF, but fibroblasts with their ability to produce matrix molecules are of special interest. Studies have shown that both the synthesis and the degradation of the ECM give rise to an ECM composition that is characteristic for fibrotic disease. In IPF, the tissue niche in the lungs contains approximately two to three times more ECM than healthy lung tissue, and the IPF fibrosis consists primarily of fibril-forming collagens (I, III, V, VI and VII), fibronectin, elastin, and proteoglycans [28] (Figure 1). Both proteases and inhibitors of those play an essential role in the degradation of the ECM. In tissues from patients with IPF, fibroblastic foci have been identified as discrete areas rich in ECM but with few cells. The cells in the fibroblast foci are arranged in an out-stretched and parallel arrangement relative to the other cells and parallel to the alveolar septa [29] (Figure 2a). It has been speculated that fibroblast foci; play a key role in the destruction of the normal lung structure, are a negative prognostic factor and lead to the progressive and irreversible disorder [29]. Interestingly, the number of circulating fibrocytes is increased in patients with IPF, and the level is further elevated in patients during an acute exacerbation [30].

A possible origin of the fibroblasts in IPF is recruitment of fibrocytes from the bone marrow. The expression of CXCR4, and its ligand SDF-1/CXCL12, is known to be up-regulated under hypoxic conditions by hypoxia-induced factor 1 α (HIF-1 α) [31,32]. The bone marrow is hypoxic as compared to the surrounding vessels, and the bone marrow expresses SDF-1/CXCL12. An injury in the lung leads to increased levels of SDF-1/CXCL12 in the plasma in bronchoalveolar lavage fluid (BALF) [33], and fibrocytes are released from the bone marrow enabling them to migrate over a chemotactic gradient to the injured lung, where SDF-1/CXCL12 is expressed [34]. The fibrocytes express MMPs, which facilitate their transendothelial and tissue migration. Furthermore, the MMPs also act as a potential participant in the remodelling of the ECM [12].

The numbers of fibrocytes can be correlated to the structural changes in all three diseases. In IPF, the amounts of fibroblast/myofibroblast foci are a negative prognostic factor, the more foci, the worse the prognosis [35]. After normal wound healing, the fibroblasts and myofibroblasts should be reduced by apoptosis, but in IPF, and especially in fibroblast foci, the numbers of fibroblasts and myofibroblasts remain constant [36]. It has been speculated that fibroblastic foci, with their

specific milieu, have a composition of cytokines, growth factors, and tissue inhibitor of metalloproteinases (TIMP) that cause fibroblasts and myofibroblasts to become apoptosis-resistant. Therefore, the ECM is produced in excess. However, the fibrocytes identified in the lung tissue of patients with IPF are not located inside the foci, but are located in close proximity to the foci in areas with ongoing signs of inflammation [33]. Those adjacent areas would later become fibroblastic foci. One could speculate that fibrocytes that have been recruited towards the fibroblast foci already have been differentiated into fibroblasts or myofibroblasts during the migration.

Asthma

The remodelling and accumulation of ECM are also histological features of asthma, where many cell types with different features are involved. The structural cells involved in asthma include epithelial cells, smooth muscle cells, and (myo)fibroblasts. The fibrosis, and for asthma characteristic tissue niche, is subepithelial. There is a thickening of the lamina reticularis which contains collagens I, III, IV, VI, tenascin, and fibronectin [37-40]. This location is also abundant in fibroblasts and myofibroblasts in the asthma patient, while the proteoglycans, versican, biglycan, and decorin, accumulate in the sub-mucosa below the epithelium in bronchial biopsies from asthma patients [38] (Figure 2b).

Nihlberg *et al.* have shown that there is both a central and a distal shift of the ECM composition, such as increased levels of versican and collagen, which the fibrocytes have to pass when they are recruited from the blood to the injured part of the lung. [22]. There, in the injured area, cytokines such as TGF- β , which are bound to the ECM, transform the fibrocytes to matrix-producing (myo)fibroblasts. Patients with chronic persistent obstructive asthma have higher levels of TGF- β and increased numbers of circulating fibrocytes than patients with asthma who have no loss of lung function [41].

A common technique to study fibrocytes *in vitro* is to cultivate them on fibronectin coated dishes, which allows the fibrocytes to attach to make further detailed analysis on biological activity and behaviour of these cells. Those type of studies have been performed of circulating fibrocytes from asthmatic patients, IPF patients, and healthy controls [9,20,42]. However, there are many questions to be solved concerning fibronectins' possibility to affect fibrocytes and the role of fibronectins in the tissue niche in these diseases [43].

Nihlberg *et al.* identified fibrocytes beneath the lamina reticularis in bronchial biopsies from patients with mild asthma, and the number of fibrocytes was correlated with the thickness of the basement membrane. The asthmatic patients were divided as to whether fibroblast-like cells could, or could not, be established from BALF.

The patients with fibroblast-like cells from BALF showed both more fibrocytes in the tissue and increased numbers of eosinophils in BALF. It is possible that this is a result of an ongoing inflammation that contributes to fibrocyte recruitment [44].

Obliterative bronchiolitis

Obliterative bronchiolitis (OB) is a common consequence of both lung transplantation and bone marrow transplantation (affecting 60% and 6%, respectively) [45,46]. The tissue process starts with lymphocyte infiltration in the submucosa and injury of the mucosa and epithelial cell layer, and that results in recruitment of ECM-producing fibroblasts or their progenitor cells, such as fibrocytes. Histologically, the rejection is seen as an ECM plug with few fibroblasts in the bronchioles [24-26] (Figure 2c). The growth factors involved in the fibro-proliferative phase of the chronic rejection are platelet-derived growth factor (PDGF) [47] and TGF- β [48], which are known to up-regulate ECM deposition.

We found that at six months after lung transplantation the lung-tissue niche was changed. Versican and decorin production by fibroblasts was increased. After TGF- β stimulation, the fibroblasts produced even higher levels of versican and biglycan in patients that went on to develop OB as compared with patients without any signs of rejections [49].

There is a thickening of the alveolar parenchyma in patients with OB after lung or bone marrow transplantation. Furthermore, there is a correlation between the thickening and the greater number of fibrocytes in the tissue. Thickening of the parenchyma could give reduced lung function which is a criterion for OB. The vessels in OB patients are also remodelled in terms of increased amounts of endothelial layer and size of the lumen. There is a correlation between the remodelled vessels and the greater number of fibrocytes in the tissue [27].

The common denominators of the remodelling are fibrocytes – and, more speculatively, local hypoxia

The interactions between HIF-1 α and HIF-1 β , SDF-1 and CXCR4, VEGF and VEGFR during angiogenesis and hypoxia are known to be important in many diseases, including fibrotic disorders. The two subunits, HIF-1 α and HIF-1 β , together form a transcription factor that regulates expression of about 100 genes that are important in mechanisms such as anaerobic metabolism, angiogenesis, and apoptosis [50]. Under normal oxygen levels, HIF-1 α is degraded and the complex with HIF-1 β does not occur. Hypoxia increases the expression of SDF-1 in endothelial cells, epithelial cells, and in cells that are in stress after an injury. Furthermore, expression of its receptor, CXCR4 [51], is also elevated. A number of cells are known to express CXCR4 on their

surfaces: fibrocytes, lymphocytes, muscle cells, and endothelial progenitor cells. Likewise, the expression of VEGF and its receptor, VEGFR, is also up-regulated to promote angiogenesis. The remodelled vessels, with enlarged lumen and greater endothelial cell area, that are identified in patients with OB after lung or bone marrow transplantation could in fact be a result of local hypoxia. Furthermore, an enlarged vessel gives a larger entrance area for the fibrocyte. The number of cells that co-express prolyl 4-hydroxylase and VEGFR2 is higher in patients with OB than in control individuals, and further, there is a correlation with the number of fibrocytes identified in the tissue (unpublished data). In asthma and IPF, vessel remodelling has also been studied, and in both diseases angiogenesis is involved that could be driven by hypoxic forces. In asthma, the vessels located in the bronchia and in the small airways are increased in number. In IPF the angiogenesis is dependent on an imbalance between IL-8 which is angiogenic, and IFN- γ , which is angiostatic [52-54].

Fibrocytes in the lumen of the airway

After the fibrocytes have entered the tissue, the fibrocytes can differentiate into other cell types and/or continue to migrate to the lumen of the airway. Asthmatic patients and IPF patients differ regarding the types of cells found in the BALF. In asthmatic patients, a relatively high proportion of the fibroblast population expresses fibrocyte markers such as CD34, CD45RO, and α -SMA [44]. In the IPF patients, 1.0-3.4% of the cells were of mesenchymal origin. It is possible that this cell population is of fibrocytic origin but has differentiated because of the local environment in the IPF lung, and for this reason does not express CXCR4 (Figure 1). We are still missing data about fibrocytes in BALF from patients with OB. The pathophysiological obliteration of the small airways probably makes it difficult for fibrocytes to migrate to the lumen, at least in the occluded part of the lung.

Conclusions

Each of the three diseases, asthma, IPF and OB, has its own specific local niche that influences the fibrocyte phenotype. In IPF, there is a correlation between the number of fibrocytes in the tissue and the number of fibroblastic foci. In asthma, thicker basement membranes are accompanied by fibrocytes in the BALF. In OB, there is a correlation between the number of fibrocytes and both vessel remodelling and thickening of the alveolar parenchyma. The fibrocytes can differentiate into fibroblasts which produce ECM molecules which further create or preserve each disorder's specific niche. Even though we still do not know to what degree the fibrocytes contribute to each disease, it might be of

interest to inhibit recruitment and differentiation of fibrocytes because they are associated with pathological airway remodelling.

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Authors' contributions

All authors wrote and revised the manuscript, and approved the final version.

Competing interests

The authors declared that they have no competing interests.

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