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Fibrocytes and fibroblasts—Where are we now

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ABSTRACT

Fibroblasts are considered major contributors to the process of fibrogenesis and the progression of matrix deposition and tissue distortion in fibrotic diseases such as Pulmonary Fibrosis. Recent discovery of the fibrocyte, a circulating possible precursor cell to the tissue fibroblast in fibrosis, has raised issues regarding the characterization of fibrocytes with respect to their morphology, growth characteristics *in vitro*, their biological role *in vivo* and their potential utility as a biomarker and/ or treatment target in various human diseases. Characterization studies of the fibrocyte continue as does emerging conflicting data concerning the relationship to or with the lung fibroblast. The source of signals that direct the traffic of these cells, as well as their response to therapeutic intervention with newly available drugs, bring new insights to the understanding of this cell type. The identification of exosomes from fibrocytes that can affect resident fibroblast activities suggest mechanisms of their influence on pathogenesis. Moreover, interesting comparisons with other pathologies are emerging involving the influence of circulating mesenchymal precursor cells on tissue responses.

1. Introduction

The description of fibrocytes in 1994 by Bucala et al. (1994) marks the beginning of an expanding field of discovery about these fibroblast-like cells, derived from the bone marrow and identified as a circulating mesenchymal cell precursor. Since this initial discovery, there have been an increasing number of studies done on the characterization of fibrocytes with respect to their morphology, growth characteristics *in vitro*, their biological role *in vivo* and their potential utility as a biomarker and/or treatment target in various human diseases including asthma, fibrosis of lung, liver and kidney, along with systemic fibrosis and atherosclerosis, to name a few.

2. Characteristics of fibrocytes

Fibrocytes, which originate from bone marrow, bear characteristics of both fibroblasts and monocytes, and hence exhibit a combination of connective tissue cell and myeloid features (Herzog and Bucala, 2010). Fibrocytes express the stem cell marker CD34, the pan-haematopoietic marker CD45, monocyte markers including CD14 and CD11 and produce components of the connective tissue matrix, such as collagen-I, collagen-III and vimentin (Herzog and Bucala, 2010). Mature fibrocytes express markers of both haematopoietic cells (CD34, CD43, CD68, CD164, CD45, LSP-1, MHC class II) and stromal cells (Pilling et al., 2009). To differentiate between fibrocytes and fibroblasts, there are at least 6 commercial reagents available which allow detection of cellular fibronectin, CD90, TE-7, CD 248, HA-BP and FAP (Pilling et al., 2009). In addition, fibrocytes were demonstrated to assume an irregular star (stellate) or spindle-shaped (fusiform) cell form when adherent or having migrated to sites of tissue injury (Pilling et al., 2009; Quan and Bucala, 2006; Quan et al., 2004). Consistent with the knowledge at that time, for several years, the identification of collagen production (content), together with the surface expression of CD34 and/or CD45, were used as the minimum criteria for identifying fibrocytes in culture, in tissue sections or in the circulation. That criteria still applies to this day as there is still no single marker found for fibrocytes and fibroblasts. Table 1 provides a guide on the common markers used for the identification and differentiation of fibrocytes and fibroblasts. However, the identification of fibrocytes in culture remains difficult, partly due to the plasticity of the cells.

Fibrocytes possess the ability to differentiate along mesenchymal lineages, including commitment to myofibroblasts or to adipocyte cells under different environmental cues (Hong et al., 2007), a feature distinguishing them from fibroblasts. Fibrocytes demonstrate the

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Table 1
Common markers used for the identification of fibrocytes and fibroblasts. Pilling et al. (2009) provide a more extensive list of markers present on fibrocytes and fibrobroblasts.

Markers	Fibrocytes	Fibroblasts
CD11a	Present	Absent
CD134	Present	Present
CD45	Present	Absent
CXCR4	Present	Absent
Alpha smooth muscle actin	Present	Present
Col-1	Present	Present
CD90	Absent	Present
TE-7	Absent	Present
S100A8/A9	Present	Absent
Fibronectin	Absent	Present
Vimentin	Present	Present
FAP	Absent	Present

expression of CD34, CD45, collagen and vimentin during the early phase of their departure from the bone marrow or during the early phase of culture (Gomperts and Strieter, 2007). However, they lose expression of CD34 and CD45 and increasingly gain expression of alpha smooth-muscle actin (α-SMA) to become myofibroblast-like cells under the influence of factors, such as transforming growth factor β (TGFβ) (Kage and Borok, 2012) and endothelin. Fibrocytes were also shown to differentiate to adipocytes when exposed to adipogenic induction media and are also suggested to differentiate to chondrocytes and osteoblasts when cultured under appropriate conditions (Gomperts and Strieter, 2007). Therefore, it is not surprising to note that fibrocytes have been implicated in the pathogenesis of multiple diseases and such plasticity could be a reason why it is difficult to treat certain diseases, such as idiopathic pulmonary fibrosis (IPF). Our understanding of this plasticity feature of fibrocytes remains poor despite significant research.

Philips et al demonstrated the importance of CXCR4-SDF-1/CXCL12 chemokine pathways in recruiting fibrocytes from bone marrow to the target tissue (Phillips et al., 2004). Mice with bleomycin induced pulmonary fibrosis and treated with anti-CXCL12 antibodies had significantly fewer fibrocytes migrating to the lung and showed lower levels of collagen and αSMA than mice treated with control antibodies (Phillips et al., 2004; Andersson-Sjöland et al., 2011). Griffiths et al showed a similar reduction of fibrocytes accumulating to the lung when bleomycin treated mice were given an antibody targeting CXCR4 (Griffiths et al., 2018). In addition, CXCL12, the ligand for CXCR4, as well as for CCR7, expressed on fibrocytes, has been found to be high in the lungs and blood of patients with IPF and these levels correlate with the numbers of circulating fibrocytes (Mehrad et al., 2007). The numbers also correlate with the number of lung fibrocytes seen in IPF patients. Interestingly, in this study, they found that lung fibrocytes in IPF patients possess different characteristics compared to circulating fibrocytes (Heukels et al., 2018). This finding could be significant and requires further investigation in detail if therapeutic targets in fibrotic lung diseases are desired. The differential characteristics of circulating and lung fibrocytes could provide a reason for the ineffectiveness of pirfenidone or nintedanib as a therapeutic cure for IPF patients, despite their proven capability to slow down disease progression.

Also important to note, there are other chemokine ligand-receptor pathways of fibrocyte recruitment, which includes chemokine secondary lymphoid tissue chemokine/chemokine ligand 21-CCR7 as well as CCL2-CCR2 and CCL12 (MCP5)-CCR2 (Phillips et al., 2004; Heukels et al., 2018; Gurczynski et al., 2016; Ekert et al., 2011). The existence of multiple recruitment pathways raises the question as to which pathway is activated under which environmental condition and what influences fibrocytes to take one pathway over the others. This has not yet been fully delineated.

As there are two approved drugs currently in use for the treatment of pulmonary fibrosis (nintedanib and pirfenidone), studies have been initiated to determine whether the fibrocyte population is affected by these drugs. Inomata et al examined the effect of pirfenidone treatment on accumulation of lung fibrocytes in a murine osmotic pump 7 day infusion bleomycin-induced pulmonary fibrosis model. In their study, they confirmed that the accumulation of fibrocytes in murine fibrotic lungs was reduced by treatment with pirfenidone through the inhibition of production of CCL2 and CCL12 and also through the partial inhibition of production of CXCL12 (Inomata et al., 2014). Moreover, they also found that inhibition of fibrocyte accumulation in the lungs was significant on day 14 after bleomycin administration. However, the effect of pirfenidone on fibrocyte accumulation on day 21 was less significant (Inomata et al., 2014). It is worth noting in this osmotic pump model, with a more chronic administration of bleomycin, marked lung oedema was present on day 10 in bleomycin-treated mice with increased levels of lung hydroxyproline at day 10 up to day 28, and on day 14, the extent of lung fibrosis was still under development. Nonetheless, they demonstrated that pirfenidone was able to decrease the fibrocyte pool size associated with attenuation of CCL2 and CCL12 production (Inomata et al., 2014). It is possible that pirfenidone becomes less effective after day 14 due to the plasticity of fibrocytes, where between day 14 and day 28, fibrocytes could be in their

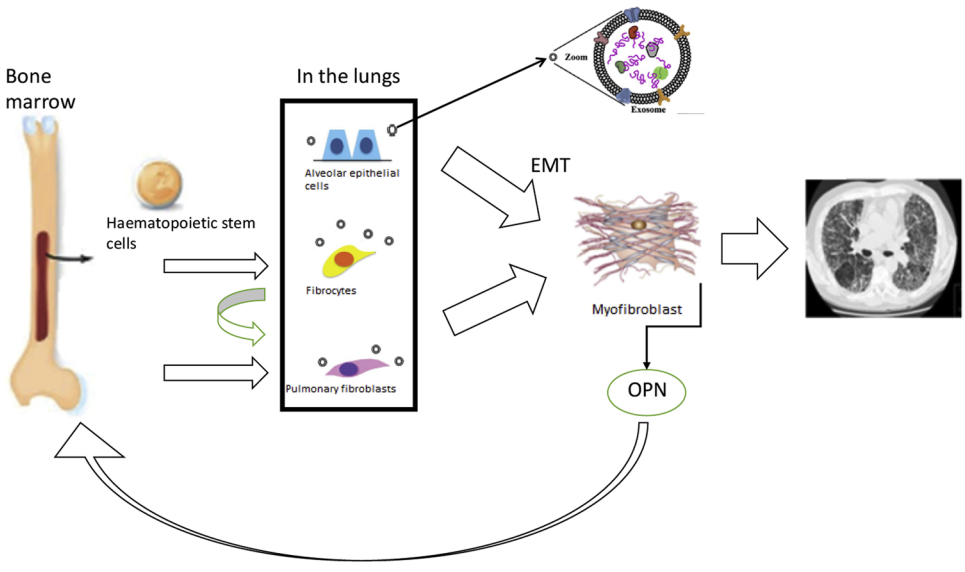

Fig. 1. The figure summarizes some of the possible events that can occur during the pathogenesis and/or progression of idiopathic pulmonary fibrosis (IPF). Circulating and lung fibrocytes are increased during the pathogenesis of IPF and they are postulated to communicate with alveolar cells to cause epithelial to mesenchymal transition (EMT) and with fibroblasts to effect transformation of fibroblasts into myofibroblasts. Damaged and activated epithelial cells and cells of the fibroblastic foci/myofibroblasts upregulate osteopontin (OPN), a glycoprotein which can active the bone marrow to release stromal precursor cells and increase profibrotic mediators in the fibrotic lungs.

transition state to myofibroblast and therefore, the effect of pirfenidone could be less. However, in this study, there was no examination of the fibrocytes between day 14 and day 28. Alternatively, another factor could come into play during prolonged fibrosis.

In another set of studies, the effect of nintedanib on fibrocytes was investigated by Sato et al (Sato et al., 2017). They showed that nintedanib inhibited the migration and differentiation of fibrocytes induced by growth factors including FGF2, PDGF-BB and VEGF-A. They also showed that nintedanib reduced the number of fibrocytes that accumulated in the mouse lung after a single intratracheal administration of bleomycin (Sato et al., 2017). However, understanding the impact of this kinase inhibitor on fibrocytes *in vivo* is restricted by limiting the examination of the lung to day 7. No information is provided about either blood or lung fibrocytes during the fibrotic phase from day 14 to day 21. It is also important to point out that most of these studies on how fibrocytes are affected by therapeutic intervention were done on animal models, but the indications of the effects of these medications on behaviour of the fibrocyte are intriguing to consider. These studies need to be replicated in human disease and the analysis of lung tissue, blood and broncho-alveolar lavage fluid from patients who were treated with pirfenidone or nintedanib should be done to provide more information on the impact on the recruitment of fibrocytes and management of fibrosis.

3. Controversies regarding fibrocytes in IPF

Fibrocytes represent 0.1–0.5% of peripheral blood leukocytes in healthy individuals (Wang et al., 2007; Chesney et al., 1997). In most experimental models, fibrocyte responses are seen in early phases of tissue injury and fibrocytes appear to be an important source of cytokines and type I collagen, during both the inflammatory and repair phase of the wound healing response, although there remain some controversies regarding this (Chesney et al., 1998; Kleaveland et al., 2014; Bianchetti et al., 2012; Kendall and Feghali-Bostwick, 2014; Hoyles et al., 2011). In a comparison study between fibrocytes and fibroblasts, it was found that the amount of newly synthesized collagen that was deposited in the extracellular matrix (ECM) over 24 h was significantly lower in cultured human fibrocytes than in cultured human fibroblasts, both in terms of absolute value and percentage of total deposited proteins (Bianchetti et al., 2012). This area of quantification of total collagen synthesis, degradation and export and deposition in ECM is one that greatly benefitted from early work from the Laurent group, where they showed that a significant proportion of newly synthesized collagen is degraded rapidly after its synthesis (probably intracellular) and that the mean turnover rates and the proportion of collagen degraded intracellularly vary widely between tissues, with lung and heart tissue amongst the highest (Laurent and McAnulty, 1983; McAnulty and Laurent, 1987). Fibrocytes were also found to constitutively express significantly lower levels of the mRNA encoding the chains of collagens I, III and V, but expressed comparable levels of the mRNA for collagen VI (Bianchetti et al., 2012), suggesting that fibrocytes may produce collagen. However, they are probably not the most important source of collagen during fibrosis, a role suggested primarily for the myofibroblast and secondly the fibroblast (Hinz et al., 2012; Phan, 2012; Lekkerkerker et al., 2012). While there is considerable agreement that bone marrow derived cells (fibrocytes) contribute to pulmonary fibrosis (Phan, 2012; Lekkerkerker et al., 2012; Lama and Phan, 2006; Rock et al., 2011; Nakashima et al., 2013), there remain several disputed issues around the pathogenesis of IPF, regarding the direct participation of fibrocytes becoming myofibroblasts or influencing resident mesenchymal cells (paracrine activation) to become myofibroblasts (Phan, 2012; Lekkerkerker et al., 2012). In renal fibrosis, Lin et al estimated that fibrocytes contribute less than 0.1% of collagen producing cells during fibrosis (Lin et al., 2008). They observed that fibrocytes appear late in renal disease and decrease in number as fibrosis progresses, raising further doubts regarding the role for fibrocytes in fibrosis. Nonetheless, the pathogenesis of renal fibrosis is dissimilar to pulmonary fibrosis. It is, however, undeniable that both fibroblasts and fibrocytes are an important source of myofibroblasts (Quan et al., 2004; Kendall and Feghali-Bostwick, 2014; Andersson-Sjoland et al., 2008).

4. Fibrocytes and cancer-associated fibroblasts

Fibroblasts are amongst the most common cell type in cancer stroma and contribute to the microenvironment critical to sustaining and possibly “protecting” the tumor. It is interesting to consider some striking similarities between the cells in the fibrotic foci in the lung, noted in IPF, to a similar relationship between a solid tumor and cancer-associated fibroblasts (Kidd et al., 2012). Notably, McAllister et al outlined a pathway of solid tumor formation that involved signalling by the primary tumor that activated the bone marrow to release stromal precursor cells (fibrocytes?) that home to a secondary tumor site to provide the microenvironment there (McAllister et al., 2008). Surprisingly, they showed that one signalling molecule released from the tumor site that activated the bone marrow was Osteopontin (OPN), a secreted glycoprotein that has pleotropic effects on inflammation, angiogenesis, fibrosis and tumor metastasis (Oh et al., 2015). This has real implications for pulmonary fibrosis, as OPN is a prominently up-regulated gene in bleomycin induced pulmonary fibrosis in mice and, importantly, in human IPF lungs (Pardo et al., 2005). In addition, OPN deficient mice have a diminished response to bleomycin induced lung fibrosis (Oh et al., 2015; Berman et al., 2004) and OPN has an inflammatory and fibrotic phenotype response both *in vitro* and *in vivo* (Oh et al., 2015; Pardo et al., 2005). Should we be looking for mechanisms involving OPN and bone marrow mobilization of fibrocytes in the pathogenesis and/or persistence of IPF (Fig. 1)?

Moreover, like the controversies associated with the source and role of the fibroblast and myofibroblast in lung fibrogenesis, there are strikingly similar debates as to whether the cancer-associated fibroblast (CAF) (Su et al., 2018) plays a beneficial or detrimental role (Su et al., 2018; Ozdemir et al., 2014), and also debates regarding the source of CAF, as coming from local stroma or from circulating bone marrow derived cells (Kidd et al., 2012; Arina et al., 2016). This is an area to watch as there may be further similarities in the therapeutic thrusts developed to understand and manage the various stromal cells and microenvironments involved.

5. Fibrocytes and exosomes

An increased number of studies in the last few years in the field of exosomes, nanovesicles of endocytic origin secreted by most cell types, has enabled us to enquire about their importance in relation to fibrocytes. This brings us back to the debate about the role of fibrocytes in collagen production during fibrogenesis. Initially regarded as cellular garbage cans to discard unwanted molecular components, newer evidence shows that exosomes act as mediators of intercellular communication by carrying proteins, lipids and genetic materials that epigenetically reprogram and alter the phenotype of their recipient cells (Chen et al., 2019; Amigorena et al., 2002). Exosomes released from fibrocytes have been demonstrated to have a dose-dependent effect on recipient cells in the expression of collagen α1 and α-SMA and showed concentration-dependent proangiogenic activity (Chen et al., 2019). Fibrocyte-derived exosomes are also enriched with miR-21, miR-142a, miR-125b, miR-126, miR-130a, and miR-132, all of which work in tandem to modulate collagen production, resulting in enhanced deposition of mature collagen fibrils in the wound and promotion of wound contraction at an early stage in the wound-healing process (Wang et al., 2012).

From the perspective of IPF, fibrocyte-derived exosomes may also facilitate epithelial to mesenchymal transition (Chong et al., 2018). Comparison of the miRNA within fibrocyte-derived exosomes,

fibroblast-derived exosomes and epithelial-derived exosomes, showed that fibrocyte-derived exosomes contain profibrotic profiles different from fibroblast-derived exosomes and/or epithelial-derived exosomes and this suggests an intricate interplay of all the cell types that contribute to the pathogenesis of fibrosis (unpublished data). It is unknown which of the miRNAs trigger the profibrotic cascade during fibrogenesis and many studies still need to be carried out in this regard.

In conclusion, there are many unsolved questions with regards to the role and characteristics of fibrocytes during the pathogenesis of IPF. Research done thus far is fragmentary and still inadequate to provide a comprehensive picture of fibrocytes and define the role they play in fibrogenesis. We need to be able to understand the regulation of fibrocyte function beyond correlating the number of fibrocytes with disease states. Studies replicating animal studies using human fibrocytes, either from blood, bronchoalveolar lavage fluid or lung tissues should be given priority. Studying the biology of fibroblasts along with fibrocytes may reveal the interactions which are essential during the pathogenesis of fibrosis.

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