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Cells in focus

Fibroblasts and myofibroblasts: Their source, function and role in disease

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Abstract

Fibroblasts are found in most tissues of the body. They exhibit several phenotypes including non-contractile fibroblasts, contractile myofibroblasts, and intermediate phenotypes including the protomyofibroblast. Fibroblasts are metabolically active cells which play critical roles regulating extracellular matrices, interstitial fluid volume and pressure, and wound healing. Fibroblast numbers can be maintained or expanded by proliferation of resident populations but in addition, recent evidence indicates they can also be derived through epithelial-mesenchymal transition or from circulating and tissue-derived mesenchymal stem cells. Many diseases are associated with dysregulation of the injury repair response and fibroblast function, leading to increased or decreased deposition of extracellular matrix proteins, altered tissue architecture, impaired function and in some cases significant morbidity and mortality. There are currently no specific therapies that target fibroblast-associated pathology but increasing knowledge of pathological mechanisms has led to development of new agents providing hope for improved treatment of these diseases.

Cell facts

- Transdifferentiates between non-contractile and contractile phenotypes
- Major cell involved in the synthesis of soft tissue extracellular matrix proteins
- Capable of producing 3.5 million molecules of collagen per cell per day
- Major producer of MMPs capable of degrading extracellular matrix
- Important role in regulating tissue hydration/osmotic pressure
- Contraction of wounds via generation of intracellular contractile forces

Keywords: Fibroblast; Myofibroblast; Mesenchymal cells; Epithelial-mesenchymal transition; Fibrocyte; Stem cells; Extracellular matrix; Fibrosis

1. Introduction

Fibroblasts are spindle shaped cells found in the majority of tissues and organs of the body associated with extracellular matrix (ECM) molecules. Characteristic features include expression of vimentin in the absence of desmin and α-smooth muscle actin. When activated,

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fibroblasts exhibit an abundant endoplasmic reticulum and prominent Golgi associated with the synthesis and secretion of ECM molecules including collagens, proteoglycans and fibronectin, as well as, proteases capable of degrading the ECM. Cytoskeletal proteins in association with cell surface integrins and the ECM facilitate cell motility and the generation of contractile forces important in tissue homeostasis and wound healing.

2. Cell origin and plasticity

Fibroblasts are embryologically of mesenchymal origin with a spectrum of phenotypic entities ranging from the non-contractile fibroblast to the contractile myofibroblast with a number of intermediate phenotypes having been described (reviewed in Eyden, 2005) including that of the protomyofibroblast (Desmouliere, Darby, & Gabbiani, 2003). In addition to the features of active fibroblasts, prototypical myofibroblasts are distinguished by the presence of α-smooth muscle actin containing stress fibres, linked in a linear fashion through trans-membrane fibronexus junctions to protruding filamentous fibronectin fibres, increased expression of ED-A fibronectin and gap junctions (for extensive reviews see Desmouliere et al., 2003; Eyden, 2005). Myofibroblasts are further distinguished from smooth muscle cells by their general lack of smooth muscle markers including desmin and smooth muscle myosin. Myofibroblasts may arise from the transdifferentiation of fibroblasts and smooth muscle cells. However, whether myofibroblast-like cells derived from fibroblasts and smooth muscle cells form similar or distinct phenotypic populations is debatable and whether fibroblasts can differentiate into smooth muscle cells and *vice versa* is uncertain, although recent studies suggest that fibroblasts can differentiate into myofibroblast-like cells with induction of protein expression patterns previously thought to be characteristic of smooth muscle cells (Chambers, Leoni, Kaminski, Laurent, & Heller, 2003). Traditionally it was thought that replacement or expansion of fibroblast/myofibroblast populations homeostatically and in wound healing or disease settings was from resident tissue populations of cells. However, over the last 10–15 years mounting evidence suggests that fibroblasts/myofibroblasts, at least following injury and in fibrotic disease, may be derived from a variety of sources. These include dedifferentiation of epithelial cells by a process known as epithelial-mesenchymal transition (EMT), as well as, bone marrow- and tissue-derived mesenchymal stem cells (Fig. 1). However, the relative contributions of each of these sources are currently a topic of intense debate due to the potential implications for therapy in wound healing, cancer and fibrosis.

2.1. Epithelial-mesenchymal transition

EMT is widely believed to occur during development and in cancer progression, however its role in the tissue response to epithelial stress or injury, at least *in vivo*, is more controversial (reviewed in Zavadil & Bottinger, 2005). The sequence of molecular events involved in EMT has recently been extensively reviewed by Zavadil and Bottinger (2005). Briefly, EMT requires the organised dedifferentiation of epithelial cells with loss of polarity, adherans and tight junctions through downregulation of proteins associated with the maintenance of these structures including ZO1, cadherins and desmoplakin through the upregulation of the *Snail/Slug* family of transcriptional repressors and switching from epithelial α6β4 to mesenchymal α5β1 integrin expression. This leads to the release of non-polarized epithelial cells with a remodelled mesenchymal stress fibre pattern of actin localisation rather than the epithelial cortical pattern of cytoskeleton. To allow transitioning cells to migrate into the interstitium, metalloproteinases (MMP), such as MMP2 and MMP9 are induced to digest the basement membrane. A number of extracellular stimuli have been shown to be involved in the induction and progression of EMT including, TGF-β, FGF-2, EGF and IGF-II (reviewed in Kalluri & Neilson, 2003). Whilst EMT has clearly been demonstrated to occur *in vitro,* it has been more difficult to prove *in vivo*. Until recently, *in vivo* evidence for EMT has relied on the demonstration of loss and gain of epithelial and mesenchymal markers, respectively, in transitioning cells. Whilst there are good markers for epithelial dedifferentiation (e.g. ZO-1, E-cadherin, desmoplakins, cytokeratin 18 and MUC1), fibroblast markers, such as vimentin, FSP1 and α-smooth muscle actin are less specific, also being expressed in other cells types or only expressed in a sub-population of fibroblasts/myofibroblasts. However, recent studies in the lungs of mice where β-galactosidase was specifically expressed in epithelial cells has provided strong evidence of transitioning of these cells into fibroblasts during the development of lung fibrosis and that these cells represented the majority of the increased number of fibroblasts in the lung, suggesting that EMT is an important source of fibroblasts, at least in the lung (Kim et al., 2006).

2.2. Bone marrow-derived stem cells

A number of studies have demonstrated the potential for bone marrow-derived circulating fibrocytes to