Mesenchymal cells emerge as primary contributors to fibrosis in multiple tissues

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Abstract A longstanding controversy exists regarding the cellular origin of myofibroblasts in tissue fibrosis. A recent study by Hung and colleagues (Am J Respir Crit Care Med 188(7):820–830, 2013) used genetic fate mapping of FoxD1 embryonic progenitor cells to show a major and direct contribution of mesenchymal cells to fibrogenesis in the lung. Future studies using FoxD1-specific inducible knockout models of pro-fibrotic genes such as CCN2 will be valuable for determining anti-fibrotic drug targets. The emergence of pericyte-like myofibroblast precursors also raises the question of whether mesenchymal stem cells in various niches contribute to fibrotic responses throughout the body.

Keywords Fibrosis · Myofibroblasts · Pericytes · Mesenchymal stem cells

Tissue fibrosis is implicated in approximately 45 % of all deaths in the Western world, yet no effective treatments exist (Wynn 2007). Myofibroblasts are the final effector cells in fibrosis, and are defined as a differentiated, contractile, and potentially invasive form of fibroblasts hallmarked by the expression of alpha-smooth muscle actin (α -SMA) (Hinz et al. 2007). Determining the cellular origin of myofibroblasts in tissue fibrosis is crucially important to understanding the progression of fibrosis and developing effective treatments for fibrotic diseases. The topic has been controversial for several years, with research implicating epithelial cells, endothelial cells, bone marrow-derived fibrocytes, and mesenchymal cells such as perivascular pericytes and resident fibroblasts all as potential origins of the myofibroblast (Quaggin and Kapus 2011). Recent studies using

genetic fate mapping tools suggest that mesenchymal cells are the primary contributors to fibrogenesis in multiple organs.

In 2008, a study published by the Duffield laboratory at the University of Washington identified FoxD1 expressing embryonic progenitor cells as precursors to mesenchymal cells in the kidney (Humphreys et al. 2010). Using genetic fate mapping techniques, the group showed that these mesenchymal cells, identified as pericytes, were a major contributor to myofibroblasts in a model of renal fibrosis. Pericytes, defined morphologically as cells directly adjacent to endothelial cells that surround blood vessels, were first suggested as a potential origin of myofibroblasts by Kristofer Rubin over a decade earlier based on their potential to migrate and develop into collagen-synthesizing fibroblasts (Sundberg et al. 1996). In a recent report by the Duffield laboratory, cell fate mapping techniques were used again to comprehensively investigate the origin of myofibroblasts in pulmonary fibrosis (Hung et al. 2013). As in the kidney, FoxD1 was found to be expressed in embryonic progenitor cells that gave rise to a large daughter population of mesenchymal cells in the adult lung of the mouse. Fate mapping showed that these daughter cells exhibited a pericyte morphology and were positive for the pericyte markers platelet-derived growth factor receptor beta (PDGFR β) and neuron-gial antigen 2 (NG2). It was also shown that these cells could exhibit functional plasticity between an immune regulating and collagen secreting phenotype, consistent with the idea that pericytes are a population of mesenchymal stem cells (Crisan et al. 2008). In response to bleomycin-induced lung fibrosis, up to 68 % of α SMA⁺ myofibroblasts were derived from the FoxD1 lineage pericytes. Furthermore, 30 % of those cells expressed type 1 collagen, suggesting that they contribute directly to the fibrotic response.

Given the apparent specificity of FoxD1 as a lineage marker for pericyte-like cells both in the kidney and lung, a next logical step appears to be the generation of FoxD1-specific inducible knockout models that target genes controlling

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fibrogenesis. The ability to successfully prevent tissue fibrosis in this manner would unequivocally demonstrate the importance of these mesenchymal cells in fibrogenesis and identify possible targets for anti-fibrotic drugs. One target gene could be CCN2, a matricellular protein characteristically overexpressed in fibroblasts during fibrosis. Its overexpression alone has also been shown to cause lung, kidney, and skin fibrosis in vivo (Sonnylal et al. 2010). CCN2 has also been shown to be required for bleomycin-induced skin fibrosis through its ability to promote differentiation of progenitor cells into myofibroblasts (Liu et al. 2011).

The emergence of pericytes as primary contributors to fibrosis in the kidney and lung also raises the question of whether mesenchymal stem cells in different niches are responsible for fibrogenesis across tissues. In cancer research there is an emerging idea of “pericyte mimicry”, prompted by the finding that a subset of melanoma cells can express the classical pericyte markers PDGFR β and NG2 and display stem cell properties (Lugassy et al. 2013). This implies that these markers are not specific to pericytes, but can be expressed by various populations of stem cells in response to environmental cues. Recent evidence suggests that skin progenitor cells (SKPs), a population of Sox2⁺ dermal stem cells with a niche in the dermal papilla of the hair follicle, are a major contributor to fibrosis in the skin (Liu et al. 2013). Although these cells are not pericytes as defined by morphology or location, the SKPs, like cancer cells, may display “pericyte mimicry” under fibrotic conditions. As such, it may be possible that fibrosis is regulated throughout the body by a common mesenchymal progenitor cell type.

Taken together, the recent study performed by Hung and colleagues builds on the body of evidence suggesting that mesenchymal progenitor cells play an important role in fibrogenesis. The door is now open to conduct in vivo promoter-specific knockout studies in order to further elucidate the mechanisms of fibrosis. Studies performed across various tissues suggest that fibrosis occurs through a dysregulation

of progenitor cell differentiation, and that targeting these pathways may be a key to developing effective anti-fibrotic therapies.

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