Heart failure is the primary cause of adult mortality in the Western world, affecting 1% to 2% of the population, including ≤10% of people >70. Several disease settings, including coronary artery disease, hypertension, diabetes mellitus, and hypertrophic cardiomyopathy, promote a maladaptive response characterized by myocyte hypertrophy and fibrosis. The latter refers to excessive extracellular matrix deposition that causes myocardial stiffening characteristic of heart failure.

Cardiac fibroblasts are the primary cell type responsible for extracellular matrix remodeling during development and in disease. In a pathological context, activation and accumulation of fibroblasts perturb normal deposition and degradation of extracellular matrix components, notably of collagen type I and causes formation of rigid fibrotic lesions within myocardium. Hence, identifying mechanisms responsible for fibroblast accumulation in the failing heart represents a key issue for development of effective antifibrotic therapies.

Recent studies have proposed that endothelial-to-mesenchymal transition (EndoMT) and recruitment of circulating progenitors generate fibroblasts responsible for cardiac fibrosis. A key marker used to identify cardiac fibroblasts in these studies was fibroblast-specific protein 1 that has been recently shown to be expressed by other cell types. Many of these studies acknowledge that resident fibroblast populations are also engaged in the process of remodeling, but some have implied that these nonresident cell populations are more pathogenic or the "bad guys," suggesting that these cells contribute significantly to inflammation and matrix production under pathological conditions. Several markers are currently used to identify cardiac fibroblasts, including-discoidin domain receptor family member 2, vimentin, fibroblast-specific protein 1, and Thy1. However, these markers are also expressed by other cell types. Immunostaining against secreted extracellular matrix proteins, including Tie2, which predominantly labels endothelial and blood lineage surface markers, Ali et al found a fibroblast population present in adult mouse myocardium at baseline derived from Tie2 lineages. Furthermore, Ali et al report elegant bone marrow transplant and parabiosis experiments, which rule out a significant contribution of hematopoietic and circulating progenitors to fibroblasts after pressure overload. These data are in contrast to previous reports, which implicated a circulating source of fibroblasts identified using a pressure overload model and, more controversially, a myocardial infarction model. From these data, Ali et al conclude that the Tie2Cre-labeled, Thy1+ fibroblasts are derived from endothelium, rather than hematopoietic or circulating progenitors to fibroblasts after pressure overload. This subset represents 20% of fibroblasts at baseline, a percentage that did not vary significantly after pressure overload. From their observations, Ali et al propose that the increased number of endothelially derived fibroblasts observed after aortic banding is primarily because of proliferation of an endogenous fibroblast population rather than recruitment of hematopoietic progenitors.
Whereas Ali et al report that Thy1+,Tie2Cre-labeled fibroblasts fibroblast-specific protein 1+ cells in hypertrophic hearts, signaling led to a decreased number of Tie1Cre lineage traced reported that inhibition of transforming growth factor-1 sig-

HE indicates hematopoietic and endothelial lineage markers. EndoMT or conversion of hematopoietic progenitors into fibroblasts. after aortic banding, leading to fibrosis. There was no evidence for EndoMT or conversion of hematopoietic progenitors into fibroblasts. HE indicates hematopoietic and endothelial lineage markers.

than de novo EndoMT, as suggested previously (Figure).3 The endothelial derived fibroblasts presented similar proliferation rates and expression profiles after aortic banding as Tbx18-Cre15-labeled epicardium-derived Thy1+HE fibroblasts in healthy myocardium. These developmentally derived subsets proliferate after aortic banding, leading to fibrosis. There was no evidence for EndoMT or conversion of hematopoietic progenitors into fibroblasts.

The study of Ali et al supports the main conclusions of an-

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Disclosures
None.

References

Figure. Previous studies have proposed that cardiac fibroblasts derive from epicardium during development, whereas large numbers of fibroblasts are generated by endothelial-to-mesenchymal transition (EndoMT) and recruitment of blood cells after pressure overload. The study by Ali et al shows that Tie2Cre-tagged Thy1+HE- fibroblasts are present alongside epicardially derived Tbx18-Cre lineage traced Thy1+HE fibroblasts in healthy myocardium. These developmentally derived subsets proliferate after aortic banding, leading to fibrosis. There was no evidence for EndoMT or conversion of hematopoietic progenitors into fibroblasts. HE indicates hematopoietic and endothelial lineage markers.

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than de novo EndoMT, as suggested previously (Figure).3 The endothelial derived fibroblasts presented similar proliferation rates and expression profiles after aortic banding as Tbx18-Cre15-labeled epicardium-derived fibroblasts, which made up 75% of the Thy1-positive fibroblast pool in control and banded animals. Ali et al also show, using Pax3-Cre tagging,25 that ~5% of cardiac fibroblasts are derived from neural crest, and that these cells reside mainly in right atrium.

These findings refute the idea that targeting EndoMT in cardiac fibrosis may be beneficial. Previously, Zeisberg et al reported that inhibition of transforming growth factor-β1 signaling led to a decreased number of Tie1Cre lineage traced fibroblast-specific protein 1+ cells in hypertrophic hearts, data that were interpreted as evidence for reduced pathologi-

5. Kong P, Christia P, Frangogiannis NG. The pathogenesis of cardiac fi-

Figure.

fibroblasts: Tbx18-Cre (epicardial) labelled Thy1+ HE fibroblasts
Tie2-Cre (endothelial/blood) labelled Thy1+ HE fibroblasts

Previous Model
Ali et al’s study
Fibroblasts:
epicardial origin
endothelial origin
hematopoietic origin
Fibroblasts:
epicardial origin
endothelial origin
hematopoietic origin

Moore-Morris et al Sorting Out Cardiac Fibroblasts


Key Words: Editorials ▪ fibroblasts ▪ fibrosis ▪ pericardium
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Thomas Moore-Morris, Michelle D. Tallquist and Sylvia M. Evans

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