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Cardiac Fibrosis: Pathobiology and Therapeutic Targets

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Abstract

Cardiac fibrosis is characteristic of the end stage in nearly all forms of heart disease. Accumulation of extracellular matrix in the myocardium leads to increased risk of arrhythmia and impaired cardiac function, and ultimately progression to heart failure. Despite the critical need to slow or reverse development of cardiac fibrosis to maintain cardiac function, there are no approved therapies that directly target the extracellular matrix. Research into the underlying causes and therapeutic targets has been hampered, in part, by the lack of a clear marker for cardiac fibroblasts – the cells responsible for regulating extracellular matrix turnover. Lineage tracing studies as well as single-cell RNA sequencing studies have provided new insights into cardiac fibroblast origins and heterogeneity. Moreover, a greater understanding of pathways governing fibroblast activation during ischemic and non-ischemic cardiac remodeling and their communication with other inflammatory and cardiac cells may lead to novel therapeutic targets to slow or reverse fibrotic remodeling. The special issue of Cellular Signaling entitled “Cardiac Fibrosis: Pathobiology and Therapeutic Targets” is comprised of review articles in which these topics, as well as important open questions for future investigation, are discussed.

Keywords

fibroblast; fibrosis; inflammation; myofibroblast; heart disease

Heart failure is a debilitating illness that affects 6.2 million Americans. A hallmark of heart failure is excessive extracellular matrix accumulation.[1, 2] Over time, this accumulation results in impaired cardiac systolic and diastolic function, as well as an increased propensity to arrhythmias and death. Fibrosis is a common end-stage characterization of nearly every type of heart disease yet there is currently no approved therapy that directly targets the excessive extracellular matrix or the cardiac fibroblasts that produce it. This is due, in

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part, to a limited understanding of the relative contribution that various cardiac fibroblast subpopulations play in the pathobiology of fibrosis.[2] Activated cardiac fibroblasts in the remodeling heart arise primarily from resident cardiac fibroblasts.[3, 4] As such, there is a great deal of interest in elucidating the roles that different resident cardiac fibroblast subpopulations play in the healthy and remodeling myocardium. In this special issue of *Cell Signalling*, the underlying mechanisms governing cardiac fibrosis as well as key therapeutic targets and important areas of future investigation are presented. The authors discuss various drivers of fibroblast activation, the coordination of immune responses and extracellular matrix production, the intracellular signals that drive gene expression in fibroblasts, maturation of extracellular matrix, as well as novel therapeutic targets for inhibiting or reversing fibrotic remodeling.

While once considered functionally homogeneous, resident cardiac fibroblasts are now known to be comprised of several sub populations of different phenotypes and functions.[5] Aujla and Kassiri review the diverse origins of cardiac fibroblasts and the various signalling pathways that lead to fibroblast activation.[6] Reichardt et al. expands on this concept as they demonstrate that fibroblast cell state is more dynamic and complex than previously thought.[7] Moreover, fibroblast state space can be altered by modulating the transforming growth factor-β (TGFβ) pathway to impact the global fibrotic response to cardiac injury, suggesting that fibroblast cell state may be a viable target for therapeutic intervention. By re-thinking the concepts of conventional fibroblast transdifferentiation paradigms[7] and understanding the relevance of fibroblast heterogeneity in mediating fibrosis in different models of heart failure[6] we will be better able to identify the signalling pathways implicated in fibroblast activation with a goal of developing novel therapeutics.

An improved understanding of the many inputs that drive fibroblast activation also provides the opportunity to identify new therapeutic targets. The immune system has been widely shown to play a role in fibrotic remodeling both in response to pressure overload and myocardial infarction. Smolgovsky, et al. review the fibrosis-inflammation axis in both non-ischemic and ischemic cardiac remodeling.[8] Immunological processes and drivers are highlighted along with the potential for immunomodulators as future therapeutic options. In response to myocardial infarction, there is a rapid inflammatory and wound healing response to maintain cardiac function. As reviewed by Daseke et al., neutrophils play critical roles during the repair process through transitions from pro-inflammatory to anti-inflammatory to reparative over the myocardial infarction time continuum.[9] The crosstalk among fibroblasts and the various immune cells to regulate fibrosis post-infarction was reviewed by Zaidi et al. as well as therapeutics that are currently under pre-clinical and clinical investigation.[10] The efficient transition from inflammatory to wound healing phases and development of a stable scar are critical for survival. However over time, ongoing inflammation and continued fibroblast activation can result in infarct expansion and impaired cardiac function. The review by Burke et al. discusses the role that resident fibroblasts play in communicating with other cells to facilitate this wound healing response in the healing infarct scar.[11] Moreover, the intercellular adhesion molecule cadherin-11 may represent a novel target given that it has been shown to promote the differentiation of activated fibroblasts and to modulate mechanical and inflammatory pathways associated

with fibrotic diseases.[12] As Riley et al. discuss, this molecule may be an important link between the biomechanical, inflammatory, and fibrotic pathways.[12]

Just as the upstream drivers of fibroblast activation exhibit significant variety, the intracellular molecular mechanisms that transduce external signals to altered fibroblast gene expression and behavior are similarly diverse. The Smad signaling pathway is arguably the most well-defined such mechanism, particularly in response to TGFβ ligand-receptor binding. The pro-fibrotic impact of the activation of Smads is well-documented not only in the heart, but throughout the body including the lungs and skin. However, despite decades of study, new discoveries in relation to this pathway continue to emerge, including the specific roles of individual Smads as reviewed by Hanna et al.[13] New and emerging intracellular signaling mechanisms continue to be identified, as Landry et al. discuss in their review of the mechanosensitive signaling pathways involving SKI and Hippo.[14] Additional pathways that may be tractable to therapeutic intervention, particularly downstream from angiotensin II as well as the long-term impacts of renin angiotensin system inhibition, are noted by Garvin et al.[15]

Activated intracellular pathways transduce extracellular signals to effector activation, including alterations in gene expression, cell function, and the secretion of extracellular matrix regulators. A critical alteration of myofibroblasts compared to fibroblasts is a sharp increase in the rate of collagen synthesis relative to the rate of degradation. A key step in collagen production is the cross-linking of collagen strands to form fully mature fibers that contribute to both healthy and fibrotic extracellular matrix, as reviewed by Neff et al.[16] Other factors found in the extracellular milieu may arise either from fibroblasts or inflammatory cell types to impact extracellular matrix structure and function, such as matrix metalloproteinases. A newer class of regulators of fibrosis are the granzymes, which can act at extracellular sites to impact fibrosis development by altering intercellular communication, as discussed by Zeglinski et al.[17]

This is an exciting time in fibrosis research: new approaches and new discoveries have together painted the most complete picture yet of how cardiac fibroblasts are activated to become myofibroblasts and drive tissue fibrosis, even as the story becomes ever more complex. As the interplay of activators, transducers and effectors of pro- and anti-fibrotic signaling are mapped, novel therapeutic targets are being identified and exploited. The arrival of new drugs for arresting, or perhaps even reversing, cardiac fibrosis seems to, finally, be relatively close-at-hand. The papers presented here bolster the reasons for optimism and provide new insight into a pathophysiology that has remained stubbornly untreatable. We hope that you enjoy this special issue.

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Abbreviations

TGFβ	transforming growth factor-β

References

[1]. Schocken DD, Benjamin EJ, Fonarow GC, Krumholz HM, Levy D, Mensah GA, Narula J, Shor ES, Young JB, Hong Y, Prevention of heart failure: a scientific statement from the American Heart Association Councils on Epidemiology and Prevention, Clinical Cardiology, Cardiovascular Nursing, and High Blood Pressure Research; Quality of Care and Outcomes Research Interdisciplinary Working Group; and Functional Genomics and Translational Biology Interdisciplinary Working Group, Circulation117(19) (2008) 2544–2565. [PubMed: 18391114]

[2]. Berk BC, Fujiwara K, Lehoux S, ECM remodeling in hypertensive heart disease, J Clin Invest. 117(3) (2007) 568–75. [PubMed: 17332884]

[3]. Kanisicak O, Khalil H, Ivey MJ, Karch J, Maliken BD, Correll RN, Brody MJ, SC JL, Aronow BJ, Tallquist MD, Molkentin JD, Genetic lineage tracing defines myofibroblast origin and function in the injured heart, Nature communications7 (2016) 12260.

[4]. Moore-Morris T, Guimaraes-Camboa N, Banerjee I, Zambon AC, Kisseleva T, Velayoudon A, Stallcup WB, Gu Y, Dalton ND, Cedenilla M, Gomez-Amaro R, Zhou B, Brenner DA, Peterson KL, Chen J, Evans SM, Resident fibroblast lineages mediate pressure overload-induced cardiac fibrosis, J Clin Invest124(7) (2014) 2921–34. [PubMed: 24937432]

[5]. Garvin AM, De Both MD, Talboom JS, Lindsey ML, Huentelman MJ, Hale TM, Transient ACE (Angiotensin-Converting Enzyme) Inhibition Suppresses Future Fibrogenic Capacity and Heterogeneity of Cardiac Fibroblast Subpopulations, Hypertension77(3) (2021) 904–918. [PubMed: 33486989]

[6]. Aujla PK, Kassiri Z, Diverse origins and activation of fibroblasts in cardiac fibrosis, Cellular signalling78 (2021) 109869. [PubMed: 33278559]

[7]. Reichardt IM, Robeson KZ, Regnier M, Davis J, Controlling cardiac fibrosis through fibroblast state space modulation, Cellular signalling79 (2021) 109888. [PubMed: 33340659]

[8]. Smolgovsky S, Ibeh U, Tamayo TP, Alcaide P, Adding insult to injury - Inflammation at the heart of cardiac fibrosis, Cellular signalling77 (2021) 109828. [PubMed: 33166625]

[9]. Daseke MJ, Chalise U, Becirovic-Agic M, Salomon JD, Cook LM, Case AJ, Lindsey ML, Neutrophil signaling during myocardial infarction wound repair, Cellular signalling77 (2021) 109816. [PubMed: 33122000]

[10]. Zaidi Y, Aguilar EG, Troncoso M, Ilatovskaya DV, DeLeon-Pennell KY, Immune regulation of cardiac fibrosis post myocardial infarction, Cellular signalling77 (2021) 109837. [PubMed: 33207261]

[11]. Burke RM, Burgos Villar KN, Small EM, Fibroblast contributions to ischemic cardiac remodeling, Cellular signalling77 (2021) 109824. [PubMed: 33144186]

[12]. Riley LA, Merryman WD, Cadherin-11 and cardiac fibrosis: A common target for a common pathology, Cellular signalling78 (2021) 109876. [PubMed: 33285242]

[13]. Hanna A, Humeres C, Frangogiannis NG, The role of Smad signaling cascades in cardiac fibrosis, Cellular signalling77 (2021) 109826. [PubMed: 33160018]

[14]. Landry NM, Dixon IMC, Fibroblast mechanosensing, SKI and Hippo signaling and the cardiac fibroblast phenotype: Looking beyond TGF-β, Cellular signalling76 (2020) 109802. [PubMed: 33017619]

[15]. Garvin AM, Khokhar BS, Czubryt MP, Hale TM, RAS inhibition in resident fibroblast biology, Cellular signalling80 (2021) 109903. [PubMed: 33370581]

[16]. Neff LS, Bradshaw AD, Cross your heart? Collagen cross-links in cardiac health and disease, Cellular signalling79 (2021) 109889. [PubMed: 33347984]

[17]. Zeglinski MR, Granville DJ, Granzymes in cardiovascular injury and disease, Cellular signalling76 (2020) 109804. [PubMed: 33035645]