Governing the Transition From Inflammation to Fibrosis in Heart Failure With Preserved Left Ventricular Function

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Cardiac remodeling is a term that broadly refers to changes in myocardial structure and function in response to injury. Irrespective of the injurious mechanism (ie, myocardial infarction, hypertensive heart disease, valvulopathy, myocarditis, or primary myocyte dysfunction), a decline in ventricular function activates several compensatory pathways designed to sustain tissue perfusion. Among these cascades, the sympathetic nervous system, the renin-angiotensin-aldosterone system, and the transforming growth factor-β (TGF-β) system stimulate myocyte hypertrophy and cardiac fibrosis. Traditionally, this paradigm of cardiac remodeling is applied to subjects with heart failure and reduced left ventricular ejection fraction; however, the precise molecular mechanisms underlying the pathophysiology of heart failure with preserved ejection fraction (HFpEF) are poorly understood.

Although much attention has focused on myocyte biology in heart failure, regulation of cardiac fibrosis in the context of HFpEF remains an area of active investigation. The cardiac fibroblast is the primary cell type responsible for generating extracellular matrix (ECM) within the myocardium. This ECM is composed primarily of type I collagen (80%) and type III collagen (10%). The remaining 10% is composed of type V and type VI collagen, laminin, elastin, glycosaminoglycans, and proteoglycans. This collagen network provides mechanical support to the myocardium, organizes muscle contraction, synthesizes and releases growth factors in a paracrine and autocrine fashion, and promotes wound healing.

The term fibrosis encompasses several processes including fibroblast proliferation, collagen synthesis and degradation, and conversion of fibroblasts into a contractile “myofibroblast” phenotype. Reparative fibrosis is characterized by replacement of myocyte loss with fibrotic tissue, whereas reactive fibrosis involves diffuse increases in interstitial ECM deposition. In response to stressful stimuli, myocardial ECM synthesis is thought to be enhanced, whereas ECM degradation is limited, thereby creating a net excess of collagen deposition. With a turnover time of 100 days, mature collagen fibrils are gradually degraded by matrix metalloproteinases (MMPs), which themselves are regulated by tissue inhibitors of metalloproteinases (TIMPs). The net effect of cardiac fibrosis is exaggerated mechanical stiffness, disorganized contraction caused by myocyte separation, disrupted electrotonic connectivity, and worsening tissue hypoxia. For these reasons, cardiac fibrosis and ECM biology remains an important target of therapy.

First identified in 1978, the cytokine TGF-β1 is a ubiquitously expressed master switch that induces the fibrotic program in various cell types including cardiac fibroblasts. In various models of heart failure, TGF-β1 expression can be induced by agonists such as angiotensin II or mechanical stretch. The cellular origin of TGF-β1 in heart failure remains unknown but may involve expression by cardiac myocytes, fibroblasts, and infiltrating monocyte/macrophages. Once secreted, TGF-β1 associates with one of several latency-associated peptides. Latent TGF-β1 can then be activated by MMP-2 and MMP-9, plasmin, thrombospondin, and the integrin αvβ6. Active TGF-β1 binds directly to its type II receptor (TBR1), which dimerizes with and activates type I receptors (TBR1), also known as activin-like kinases (ALK), for signal transduction via downstream effector proteins known as SMADs, which are mammalian homologs of the Drosophila protein mothers against decapentaplegic.

TGF-β1 induces collagen synthesis via both SMAD-dependent and SMAD-independent signaling mechanisms. The cooperative protein, SMAD-3, is central to 3 of these pathways, which include (1) direct activation of a TGF-β–response element (TRE), located in the promoter region of type I collagen (COL1A), (2) phosphorylation of activated transcription factor-2 (ATF-2) by TGF-β–activated kinase-1 (TAK1), and (3) expression of connective tissue growth factor (CTGF) via a TRE located in the CTGF promoter. Noncanonical, SMAD-independent pathways contributing to TGF-β1–induced collagen synthesis include 3 well-characterized mitogen-activated protein kinase (MAPK) cascades, including (1) p38 MAPK, (2) Jun N-terminal kinase (JNK), and (3) extracellular signal-regulated kinase (ERK). In this issue of Circulation: Heart Failure, Westermann et al provide insight into the role of cardiac inflammation as a profibrogenic stimulus in subjects with HFpEF. Their investigation of endomyocardial biopsy specimens from
these patients identified increased inflammatory cells and higher TGF-β1 mRNA levels in association with both reduced MMP-1 and elevated TIMP-1 levels, suggesting that the balance of collagen turnover favors synthesis in HfPfEF. The investigators further identify a similar profile of MMP-1/TIMP-1 expression in cardiac fibroblasts stimulated with TGF-β1 in vitro. Finally, activated THP-1 monocytes were found to express TGF-β1 in a time-dependent manner in vitro. These investigators have provided rare evidence associating increased inflammation and TGF-β1–induced collagen synthesis in human subjects with HfPfEF.

Previous studies investigating the interplay of TGF-β1 and inflammation in cardiac fibrosis have focused on models of acute myocardial infarction where a distinct inflammatory phase is followed by fibrous tissue deposition and maturation of a healing infarct. In these studies, TGF-β1 antagonism reveals the multifaceted character of TGF-β1, which stimulates tissue fibrosis and promotes myofibroblast transdifferentiation while debilitating macrophages and suppressing expression of inflammatory chemokines. Early inhibition of TGF-β1 after coronary ligation was associated with increased mortality and promoted leukocyte infiltration and chemokine expression, whereas late inhibition was associated with improved survival, reduced tissue fibrosis, and promoted contraction of the infarct zone.

Unlike acute myocardial infarction, the mechanism triggering inflammation and fibrosis in HfPfEF probably represents multifactorial stressors, including changes in hemodynamic load, metabolic derangements, and systemic endocrine disorders. Animal models of cardiac pressure overload have provided some insight into the role of TGF-β1 and inflammation in HfPfEF. After thoracic aortic constriction, inhibition of TGF-β1 attenuated cardiac fibrosis and improved diastolic function without affecting cardiac hypertrophy. Several studies have also demonstrated increased inflammation during the acute and chronic phases of pressure overload–induced heart failure. For example, increased cardiac expression of monocyte chemoattractant protein (MCP-1) has been observed after supraprenal aortic constriction and was associated with fibrosis and cardiac hypertrophy. MCP-1 expression preceded TGF-β1 upregulation and was associated with cardiac fibrosis and diastolic dysfunction. Treatment with a MCP-1–neutralizing antibody inhibited macrophage accumulation, reduced TGF-β1 expression, attenuated cardiac fibrosis, and improved diastolic function without affecting cardiac hypertrophy. Collectively, these data point toward a mechanistic link between inflammation and fibrosis that is regulated by the cytokine TGF-β1.

At present, the majority of clinical studies of inflammatory and profibrogenic mediators have focused on circulating biomarkers. In patients with heart failure, circulating levels of TNF-α, interleukin-6, interleukin-10, MCP-1, and CRP are increased and correlate with New York Heart Association functional class. Reduced circulating levels of TGF-β1 have been reported in heart failure and correlate with increased markers of inflammation. Whether reduced TGF-β1 levels represent reduced tissue concentrations or interference by circulating latency-associated peptides remains unknown and limits the clinical utility of TGF-β1 levels in heart failure. In HfPfEF, studies of ECM turnover demonstrate elevated levels of the propeptides for procollagen types 1 and 3 with increased levels of type 1 pyridinoline cross-linked C-terminal telopeptide, MMP-2, and MMP-9.

Taken together, these findings suggest active collagen turnover in HfPfEF. As identified by Westermann et al, the elusive association of inflammation and TGF-β1–induced cardiac fibrosis in HfPfEF may reveal novel diagnostic and therapeutic targets for this ever-increasing population of patients with heart failure.

Disclosures

None.

References


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