Stem Cell Factor in Mast Cells and Increased Mast Cell Density in Idiopathic and Ischemic Cardiomyopathy

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Background—We compared cardiac mast cell (HHMC) density and the immunological and nonimmunological release of mediators from mast cells isolated from heart tissue of patients with idiopathic dilated (DCM) (n=24) and ischemic cardiomyopathy (ICM) (n=10) undergoing heart transplantation and from control subjects (n=10) without cardiovascular disease.

Methods and Results—HHMC density in DCM (18.4±1.6 cells/mm²) and ICM (18.4±1.5 cells/mm²) was higher than that in control hearts (5.3±0.7 cells/mm²; P<.01). The histamine and tryptase contents of DCM and ICM hearts were higher than those of control hearts. The histamine content of the hearts was correlated with mast cell density (r=.91; P<.001). Protein A/gold staining of heart tissue revealed stem cell factor (SCF), the principal growth, differentiating, and activating factor of human mast cells, in HHMC secretory granules. Histamine release from cardiac mast cells caused by immunological (anti-IgE and rhSCF) and nonimmunological stimuli (Ca²⁺ ionophore A23187) was higher in patients with DCM and ICM compared with control subjects. Immunological activation of HHMC induced a significantly greater release of tryptase and LTC₄ in patients with DCM and ICM compared with control subjects.

Conclusions—Histamine and tryptase content and mast cell density are higher in failing hearts than in control hearts. SCF, present in secretory granules of HHMC, might represent an autocrine factor sustaining mast cell hyperplasia in heart tissue in these patients. The increased local release of fibrogenic factors (eg, histamine, tryptase, and leukotriene C₄) might contribute to collagen accumulation in the hearts of patients with cardiomyopathy. (Circulation. 1998;97:971-978.)

Key Words: cardiomyopathy ■ fibrosis ■ leukotrienes ■ cells, mast

Mast cells are the only tissue cells expressing on their surface the high-affinity receptor for IgE (FcεRI) and synthesizing vasoactive and fibrogenic factors (histamine, tryptase, and LTC₄). Mast cells are present in human heart tissue and in adventia and intima of coronary arteries of patients with coronary artery disease. Moreover, the in vitro immunological activation of human heart tissue with anti-IgE induces the release of histamine and prostaglandin D₂.

The concentration of histamine and the density of mast cells are increased in the arteries of cardiac patients and coronary arteries from cardiac patients are hyperresponsive in vitro to histamine. Furthermore, in vivo administration of histamine and other mast cell-derived mediators (peptide LTC₄) in humans causes significant cardiovascular effects. Finally, serum IgE levels are increased in patients with coronary artery disease. Taken together, these observations raise the possibility that local activation of cardiac mast cells might contribute, through the release of vasoactive mediators, to certain cardiovascular diseases.

Fibrosis is a hallmark of failing hearts in DCM and ICM. The cells and the mediators responsible for fibroblast proliferation and collagen accumulation in failing hearts in DCM and ICM are largely unknown. Mast cells are involved in many types of inflammation and repair processes and are found in increased numbers in fibrotic tissues. For example, increased mast cell density has been documented in the lesional skin of scleroderma patients and in the lung of patients with fibrotic lung disorders. A possible association between increased mast cell density and endomyocardial fibrosis was first suggested by Ferrnex in 1968. More recently, cardiac mast cells (HHMC) have been implicated in eosinophil myocarditis and in DCM secondary to systemic sclerosis. However, the studies in this area have been limited by the difficulties in isolating and purifying mast cells from human heart tissue.

We established a technique for the efficient dispersion of mast cells from human heart tissue and identified the immunological and nonimmunological stimuli that induced HHMC to release vasoactive and fibrogenic mediators in vitro. The present study was performed to compare the cardiac mast cell density, concentration of mast cell–derived mediators (histamine and tryptase), and immunological and nonimmunological release of chemical mediators from mast cells isolated from...
failing hearts obtained from patients with DCM and ICM undergoing heart transplantation and from control subjects who died in accidents. We also identified ultrastructural localization of SCF, the principal growth, differentiating, chemotactic, and activating factor for human mast cells,25–28 in cardiac tissue.

Methods

Patients

The heart tissue used in this study was obtained from patients undergoing heart transplantation at the Deutsches Herzzentrum (Berlin) and from individuals not affected by cardiovascular disease who died in accidents (control subjects).

Idiopathic DCM

Twenty men and 4 women, aged 26 to 64 years (mean age, 50.6\(\pm\)2.3 years), constituted the idiopathic DCM group. The diagnosis of DCM was based on the World Health Organization criteria29 with the demonstration of dilated and poorly contracting left and/or right ventricle in the absence of known cause. Patients were excluded from this group if there was evidence of (1) coronary heart disease at coronary arteriography, (2) ischemia during exercise testing, (3) systemic blood pressure of \(\geq\)150/90 mm Hg, (4) concomitant systemic or endocrine diseases known to cause left ventricular impairment, or (5) excessive alcohol consumption.30

Coronary Artery Disease Group

Nine men and 1 woman, aged 38 to 63 years (mean age, 49.6\(\pm\)2.7 years), constituted the ICM group. All patients had congestive heart failure and a history of acute myocardial infarction. Before transplantation, both groups of patients had been treated with multiple drugs (ACE inhibitors, cyclosporin A, digoxin, furosemide, and heparin).

Normal Donor Heart

The control subjects consisted of 9 men and 1 woman, aged 29 to 58 years (mean age, 43.4\(\pm\)3.2 years), who died from noncardiovascular
Reagents
We purchased 60% HClO4 from Baker Chemical. BSA, PIPES, hyaluronidase, collagenase type II, and synthetic LTC4 were from Sigma Chemical. Hanks’ balanced salt solution and fetal calf serum were from GIBCO. Deoxyribonuclease I and pronase were from Calbiochem. RPMI 1640 with 25 mmol/L HEPES buffer and Eagle’s minimum essential medium were from Flow Laboratories. Percoll was from Pharmacia Fine Chemicals. (3H)-LTC4 (39.3 Ci/mmol) was from New England Nuclear Research Products. Protein A/gold complex was from British Biocell International. rhSCF was from Genzyme. Rabbit anti–human-Fcε antibody was a generous gift from Drs Teruko and Kimishige Ishizaka (La Jolla Institute for Allergy and Immunology, La Jolla, Calif). The anti-peptide LTC4, antiserum was donated by Dr Keith Langley (Protein Chemistry Group, Amgen, Thousand Oaks, Calif); this antibody recognizes the region 79 to 97 of human SCF (K. Langley, personal communication). The monoclonal (hkl-12) and rabbit polyclonal anti-rhSCF antibodies were kindly provided by Dr Manfred Brockhaus (Hoffman-LaRoche, Basel, Switzerland). The monoclonal hkl-12 recognizes epitopes in the region 150 to 164 (M. Brockhaus, personal communication). The polyclonal sheep anti-human SCF was obtained from Genzyme. Irrelevant monoclonal mouse anti–E-selectin was from R&D Systems. Rabbit and sheep polyclonal IgGs from nonimmunized animals were obtained from Sigma Chemical. The tryptase RIA kit (Pharmacia Tryptase RIACT 50; Pharmacia Diagnostics AB) was kindly donated by Kabi Pharmacia SpA (Milan, Italy).

Buffers
The PIPES buffer used in these experiments was made up of 25 mmol/L PIPES, pH 7.37, 110 mmol/L NaCl, and 5 mmol/L KCl; the mixture is referred to as P. P2CG contains, in addition to P, 2 mmol/L CaCl2 and 1 g/L dextrose.32 PGMD contains 0.25 g/L MgCl2 6H2O, 10 mg/L DNase, and 1 g/L gelatin in addition to P, pH 7.37.

Isolation and Partial Purification of Human Heart Mast Cells
The explanted hearts and the hearts from subjects who died in accidents were immediately immersed in cold (4°C) cardioplegic solution, shipped by air (4°C), and processed within 5 to 18 hours of removal. The heart tissue (100 to 600 g) was placed in a beaker (Nalgene) containing buffer P at 22°C. Hearts were dissected to separate the left and right ventricles and the septum. Two small samples (∼2 g) representative of all myocardial layers of each section

Figure 4. Correlation between the histamine content of left ventricle and mast cell density of heart tissue from control subjects (●) and patients with DCM (○) or ICM (▲).

Figure 5. A, Immunogold staining for SCF of a human heart mast cell from a patient with DCM. Sections were stained for SCF (monoclonal antibody 7H6 anti-human SCF) as described in “Methods.” Gold particles that locate SCF are present over all secretory granules of the mast cell (see inset) (uranyl acetate and lead citrate stained). Bar scale, 1.1 μm. B, On higher magnification of the inset, the subcellular localization of SCF of secretory granules is seen. Gold particles are absent in the perigranular cytoplasm (uranyl acetate and lead citrate stained). Bar scale, 0.4 μm.
were obtained for microscopic examination of tissue mast cells and for measurement of total histamine and tryptase content. Fat tissue, large vessels, and pericardium were removed. HHMC were isolated from human heart tissue through the use of a technique recently described in detail. HHMC were partially purified through flotation through a discontinuous Percoll gradient as detailed elsewhere. The purity of these populations ranged from 0.2% to 18%. The viability of mast cells was routinely evaluated, and it was always >95%, as detected by Trypan blue exclusion.

Measurement of Histamine Content and Mast Cell Density of Heart Tissues

Samples of human hearts were separated from fat and large vessels through blunt dissection. For each heart, samples were obtained from left and right ventricles and septum. Tissue samples were weighed and boiled in 8% of HClO4 for 30 minutes. The mixture was filtered to remove particles, and supernatants were assayed for histamine. Samples of human hearts were separated from fat and large vessels, and pericardium were removed. HHMC were isolated from human heart tissue through the use of a technique recently described in detail. HHMC were partially purified through flotation through a discontinuous Percoll gradient as detailed elsewhere. The purity of these populations ranged from 0.2% to 18%. The viability of mast cells was routinely evaluated, and it was always >95%, as detected by Trypan blue exclusion.

Histamine Release Assay

Cells (~3×10⁶ mast cells per tube) resuspended in 0.3 mL of P2CG were placed in 12×75-mm polyethylene tubes; 0.2 mL of each prewarmed releasing stimulus was added, and incubation was continued at 37°C for 45 minutes. Each experimental group was performed in duplicate. Cell-free supernatants were stored at −70°C for subsequent assay of histamine, tryptase, and LTC4. The cell-free supernatants were assayed for histamine with the use of an automated fluorometric technique. To calculate histamine release as a percentage of total cellular histamine, the “spontaneous” release of histamine from mast cells (3% to 12% of the total cellular histamine) was subtracted from both numerator and denominator. All values are based on means of duplicate or triplicate determinations. Replicates differed from each other in histamine content by <10%.

RIA of Tryptase and LTC4

Total tryptase content was assessed by lysis induced by incubation of cells with 100 μL of Triton X-100 (0.1%). Tryptase was analyzed by a solid-phase RIA (Tryptase RIACT 50; Pharmacia). In some experiments, 200-μL fractions were taken from the supernatant fluids for the analysis of LTC4. The samples were stored at −70°C until analyzed for eicosanoid content. The LTC4 assay was carried out with a previously described RIA.

Ultrastructural Study

Samples for ultrastructural study were fixed in Karnovsky solution (0.5% glutaraldehyde, 2% paraformaldehyde in Na-cacodylate buffer, pH 7.3, 0.1 mol/L) at 4°C for 2 hours, rinsed in Na-cacodylate buffer, postfixed with 1% osmium tetroxide in 0.1 mol/L cacodylate buffer for 1 hour at 4°C, dehydrated in ethanol and propylene-oxide, and embedded in Epon-Araldite. Ultrathin sections were stained with uranyl acetate and Reynold’s lead citrate. The stained sections were examined with a Zeiss EM10 electron microscope.

Electron Microscopic Immunocytochemistry Study

Ultrathin sections were deosmicated in aqueous saturated solution of 5% sodium metaperiodate for 10 minutes, rinsed in 1% OVA in 0.01 mol/L Tris buffer and 0.5 mol/L NaCl, pH 7.6 (TBS/Triton buffer), and washed for 1 hour in TBS/Triton/l lysine buffer; the sections were then incubated with 10% heat-inactivated normal goat serum and subsequently incubated overnight with the anti-SCF antiserum (7H6) diluted 1:100 in TBS/1% BSA/0.5% sodium azide buffer. The sections were washed three times in TBS/1% BSA/0.5% sodium azide buffer for 10 minutes and incubated for 1 hour with protein A/gold complex diluted 1:30 with TBS/1% BSA/0.5% sodium azide buffer.
Mast Cells in Cardiomyopathy

Ultrastructural Features and Density of Cardiac Mast Cells in Cardiomyopathy

Human hearts obtained from patients with DCM (n=24) or ICM (n=10) undergoing heart transplantation and from subjects who died from noncardiovascular causes (n=10) were studied by gross examination, histopathology, and electron microscopy. The hearts from the control subjects were designated “normal” on gross examination and histopathology. Microscopic examination of sections stained with toluidine blue and electron microscopic studies of hearts revealed the presence of mast cells, mainly around blood vessels and between myocardial fibers in all preparations from the control, DCM, and ICM groups. Mast cells were also found in the intima of atherosclerotic lesions, as reported previously.6,9 Mast cells in human hearts were pleomorphic with respect to shape. Some mast cells were large and round or oval (62%) and were almost completely filled with cytoplasmic granules; other mast cells were slender and elongated (38%) (Fig 1). Cytoplasmic contents were dominated by numerous, membrane-bound heterogeneous (scrolls, homogeneously dense and crystals) granules and non–membrane-bound lipid bodies. In situ examination of mast cells from DCM and ICM revealed a small percentage (~5%) of activated (ie, partially degranulated mast cells), as reported previously.2,4 The mast cell density of heart tissue (left ventricle) from patients with DCM (18.4±1.6 mast cells/mm³) and ICM (18.4±1.5 mast cells/mm³) was higher than that from control subjects (5.3±0.7 mast cells/mm³) (P<.01) (Fig 2). Similar results were obtained when the right ventricles or septum were examined (data not shown).

Statistical Analysis

The results are mean±SEM. The data subjected to linear regression were calculated with the least-squares method (y=ax+bx), where a is the y-axis intercept, and b is the slope of the line. The rank correlations were calculated with the Spearman rank coefficient (r). The multiple comparisons between groups were assessed using the Student’s t test with Bonferroni’s correction for multiple comparisons.38

Results

Ultrastructural Features and Density of Cardiac Mast Cells in Cardiomyopathy

Expression of SCF in Mast Cells of Failing Human Hearts

In an attempt to explain the increased mast cell density in patients with DCM and ICM, we evaluated the presence of SCF in human heart tissue because this cytokine is the main growth and differentiating factor of human mast cells.25–28 We used a monoclonal antibody against region 79 to 97 of human SCF to detect SCF in HHMC. After protein A/gold staining of mast cells from DCM and ICM revealed a small percentage (~5%) of activated (ie, partially degranulated mast cells), as reported previously.2,4 The mast cell density of heart tissue (left ventricle) from patients with DCM (18.4±1.6 mast cells/mm³) and ICM (18.4±1.5 mast cells/mm³) was higher than that from control subjects (5.3±0.7 mast cells/mm³) (P<.01) (Fig 2). Similar results were obtained when the right ventricles or septum were examined (data not shown).

Histamine Content of Heart in Idiopathic DCM and ICM

The histamine content of left ventricles of control subjects (1.07±0.23 µg/g wet tissue) was significantly lower than those of patients with DCM and ICM (5.8±0.7 and 5.9±0.5 µg/g wet tissue, respectively; P<.05) (Fig 3). There was a significant correlation between the histamine content of human hearts and the cardiac mast cell density (r=.91; P<.001) (Fig 4), suggesting that mast cells are the main, if not the only, source of histamine in human heart tissue in control subjects and patients with cardiomyopathies. Similar findings were obtained with the right ventricle and septum (data not shown).

Expression of SCF in Mast Cells of Failing Human Hearts

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to 164 of SCF (data not shown). Granules of HHMC incubated with a murine myeloma against an irrelevant antigen or an IgG from nonimmunized rabbit or from nonimmunized sheep at concentrations similar to those of the specific antibody lacked particles. Similar results were obtained when the specific antibodies anti-SCF were neutralized with rhSCF (3 μg/mL) (data not shown).

**Mediator Release From Isolated Cardiac Mast Cells Induced by Immunological Stimuli**

SCF exerts its biological activities via interaction with c-kit, its cognate receptor present on human skin,36 lung,37 and heart mast cells24,31 and induces histamine release from these cells.3,24,26,37 We evaluated the effect of rhSCF (3X10⁻¹⁰ to 30 ng/mL) on histamine release from HHMC isolated from control subjects and DCM and ICM patients. rhSCF concentration-dependently induced more histamine release from HHMC obtained from failing heart than from control subjects (Fig 6A). The percentages of histamine release induced by rhSCF from HHMC isolated from control subjects and DCM and ICM patients were comparable (Fig 6B). Serum levels of IgE antibodies are increased in the circulation of patients with cardiovascular diseases.13,14 A polyclonal antibody against the Feε portion of IgE cased a concentration-related (3X10⁻¹⁰ to 5 μg/mL) histamine release from HHMC from control subjects and DCM and ICM patients. In these experiments, the percent histamine did not vary among the three groups examined; however, when the absolute level of release was correlated per gram of wet tissue, the difference was highly significant (Fig 7).

**Mediator Release From Isolated Cardiac Mast Cells Induced by Nonimmunological Stimuli**

The Ca²⁺ ionophore A23187 induces histamine release from mast cells presumably by increasing the intracellular concentration of Ca²⁺.24 A23187 caused a significantly higher release of histamine from HHMC from DCM and ICM patients than from control subjects. As previously noted for immunological stimuli, the percent release of histamine was similar in DCM and ICM patients (data not shown).

**Tryptase Content in the Failing Heart**

Tryptase, a neutral protease stored in the cytoplasmic granules of all human mast cells,24,32,38 can be released from human mast cells24,31 and is a potent mitogen for human fibroblasts.39 The tryptase content of heart tissue from patients with DCM and ICM patients (data not shown).

**Tryptase and LTC₄ Release From Isolated Cardiac Mast Cells Induced by Immunological Stimuli**

Peptide LTC₄ is the principal 5-lipoxygenase metabolite synthesized by HHMC,34 and it induces fibroblast proliferation.40 We therefore examined the immunological release of LTC₄ and tryptase from HHMC obtained from patients with DCM (n=4) or ICM (n=4) and in control subjects (n=4). In these experiments, IgE cross-linking induced significantly more release of tryptase (Fig 8) and LTC₄ (Fig 9) from HHMC obtained from DCM and ICM patients compared with that from control subjects.

**Discussion**

We demonstrate that the density of HHMC is markedly increased in patients with idiopathic DCM and ICM. Moreover, the release of vasoactive and proinflammatory mediators caused by immunological, cytokine, and nonimmunological stimuli is higher in DCM and ICM than in control subjects. In addition, we provide the first evidence that the secretory granules of cardiac mast cells store SCF, which is the principal cytokine inducing growth, differentiation, chemotaxis, and activation of human mast cells.25-28,36

Mast cells are the only cells in connective tissues that possess high-affinity receptors for IgE and synthesize a variety of vasoactive and fibrogenic mediators1 and proinflammatory cytokines.41-43 Mast cells and their mediators have been implicated in several disorders involving the human heart. Mast cell density is increased in the coronary arteries of cardiac patients,1-3,5 and coronary arteries from patients with ischemic heart disease are hyperresponsive in vitro to histamine.4 Furthermore, in vivo administration of histamine causes coronary spasm in 30% of patient with unstable angina.11 The presence of mast cells around4,5 and within46 coronary blood vessels suggests that local activation of cardiac mast cells might contribute, through the release of vasoactive mediators, to the pathophysiology of ischemic heart disease.43

Even more suggestive is the role of mast cells in various aspects of fibrotic lesions of the human heart. Mast cell density is increased in myocardial fibrosis in Africans29 and in DCM secondary to systemic sclerosis.33 The mechanism linking mast cells to collagen accumulation and fibrosis is complex and largely unknown. However, mast cell–derived mediators (ie, histamine, tryptase, and LTC₄) are mitogens and comitogens for human fibroblasts39,40,44,45; they stimulate collagen synthesis, and collagen accumulation is a hallmark of ICM and idiopathic DCM.17 Finally, SCF, a major product of human fibroblasts,46 is a principal growth, differentiating, chemotactic, and activating factor for human mast cells.25-28,36 These observations raise the possibility that cardiac mast cells might play a role in the fibrotic cascade in cardiomyopathy.

The increased cardiac mast cell density in patients with failing hearts may result from in situ differentiation from mast cell precursors, in situ replication from preexisting mast cells, and migration from other sites. Our data do not allow us to distinguish between these possibilities; however, SCF, also termed “mast cell growth factor,” c-kit ligand (KL), or steel factor, is the principal growth, differentiating, chemotactic, and activating factor for human mast cells.25-28,36 SCF produced by mesenchymal cells (fibroblasts, epithelial cells, endothelial cells, keratinocytes, neurons, and so on)46-49 exerts its biological activities via interaction with c-kit, its cognate receptor.46-47 The SCF receptor is a transmembrane tyrosine kinase receptor of fundamental importance for the normal development, maturation, and functioning of mast cells.28-28 The SCF receptor is expressed on the plasma membrane of mast cells.26,37 A novel finding of our study is the subcellular localization of SCF in secretory granules of HHMC. The gene for human SCF consists of at least eight exons. Alternative RNA splicing gives
rise to two SCF transcripts: one that contains sequences representing all exons (exon 6) (SCF<sup>6+</sup>) and a second, from which exon 6 is excluded (exon 6) (SCF<sup>6−</sup>).<sup>50</sup> SCF translated from exon 6 transcripts lacks the major proteolytic cleavage site. As a result, SCF<sup>6−</sup> is inefficiently cleaved at an alternative site and resides almost exclusively in the plasma membrane.<sup>50</sup> Here, we demonstrate that SCF is contained in the cytoplasmic secretory granules of HHMC. The specificity of this observation is supported by results obtained with two different monoclonal and two polyclonal anti-SCF antibodies, which presumably recognize different epitopes of human rhSCF. Thus, it is unlikely that different anti-human SCF monoclonal and polyclonal antibodies recognize cross-reactive epitopes present in secretory granules of HHMC.

Internalization of c-kit together with SCF has been demonstrated recently on human fetal liver–derived mast cells.<sup>52</sup> Moreover, SCF protein has been detected bound to skin mast cells in lesions of patients with urticaria pigmentosa.<sup>47</sup> Although we have not demonstrated SCF synthesis by human mast cells, we show for the first time that mature mast cells express SCF in their secretory granules.

In addition to providing the first ultrastructural localization of granule-associated cytokine in HHMC, this observation raises the intriguing possibility that SCFs present in the secretory granules of HHMC represents an autocrine factor that contributes to mast cell hyperplasia in failing human hearts. The increased density of cardiac mast cells and the increased local release of factors mitogenic for fibroblast (eg, histamine, tryptase, LTC<sub>4</sub>, and so on) might explain the collagen overproduction and accumulation in failing hearts.<sup>17</sup>

Several clinically relevant stimuli activate HHMC isolated from DCM, ICM, and control subjects. Serum IgE levels are increased in patients with several cardiovascular diseases,<sup>3,14</sup> and anti-IgE induces the release of preformed (histamine and tryptase) and de novo synthesized (LTC<sub>4</sub>) mediators from cardiac mast cells. Moreover, SCF, a cytokine synthesized by fibroblasts<sup>46</sup> that induces mast cell growth in vitro<sup>25,27</sup> and in vivo<sup>28</sup>, activates HHMC. These stimuli caused the same percentage of mediator release from HHMC isolated from normal and failing hearts. However, given the higher density of mast cells in DCM and ICM compared with that in control subjects, the absolute release per gram of wet tissue is significantly increased in the group of failing hearts. Enhanced release of cardiac mast cell mediators in DCM and ICM also occurred when cells were activated by such nonimmunological stimuli as A23187.

In conclusion, our results demonstrate that the histamine and tryptase content and cardiac mast cell density are markedly increased in patients with either of two different cardiomyopathies compared with control subjects. In addition, the immunological and nonimmunological release of mast cell–derived mediators from mast cells isolated from failing hearts is higher than that in the control group. SCF, identified for the first time in secretory granules of HHMC, might act as an autocrine factor that sustains mast cell hyperplasia and modulates mast cell function in heart tissue of patients with cardiomyopathy. These findings suggest that increased local release of mast cell–derived fibrogenic factor (eg, histamine, tryptase, and LTC<sub>4</sub>) could play a role in the fibrotic cascade in idiopathic DCM and ICM.

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