Cardiac Nonmyocytes in the Hub of Cardiac Hypertrophy

Takehiro Kamo, Hiroshi Akazawa, Issei Komuro

**Abstract:** Cardiac hypertrophy is characterized by complex multicellular alterations, such as cardiomyocyte growth, angiogenesis, fibrosis, and inflammation. The heart consists of myocytes and nonmyocytes, such as fibroblasts, vascular cells, and blood cells, and these cells communicate with each other directly or indirectly via a variety of autocrine or paracrine mediators. Accumulating evidence has suggested that nonmyocytes actively participate in the development of cardiac hypertrophy. In this review, recent progress in our understanding of the importance of nonmyocytes as a hub for induction of cardiac hypertrophy is summarized with an emphasis on the contribution of noncontact communication mediated by diffusible factors between cardiomyocytes and nonmyocytes in the heart. *(Circ Res. 2015;117:89-98. DOI: 10.1161/CIRCRESAHA.117.305349.)*

**Key Words:** angiogenesis factor ■ cardiac myocytes ■ endothelial cells ■ fibroblasts ■ macrophages

**Cardiac Endothelial Cells**

**Myocardial Angiogenesis and Cardiac Hypertrophy**

In the heart, endothelium lines the coronary blood vessels and the cardiac chambers, and functions not only as a structural barrier between the blood and the walls of vessels or chambers, but also as dynamic sensor and modulator for myocardial structure and function. Cardiac endothelial cells regulate coronary vascular tone by secreting a wide variety of vasoconstrictive and vasodilative factors, such as nitric oxide (NO), endothelin-1 (ET-1), and prostaglandins, and various growth factors, such as vascular endothelial growth factor, fibroblast growth factors (FGFs), and platelet-derived growth factors. Furthermore, cardiac endothelial cells play an important role in induction of cardiomyocyte hypertrophy.

Accumulating evidence suggests that angiogenesis controls the growth and size of adult organs, such as adipose tissue, liver, endocrine organ, and heart. In response to hypertrophic stimulation, the myocardium secretes angiogenic growth factors, and coordinated vascular growth enables blood supply sufficient to accommodate the increase in myocardial mass and performance. Interestingly, stimulation of myocardial angiogenesis by transgenic overexpression of PR39 or placental growth factor induced cardiac hypertrophy even in the absence of hypertrophic stimulations. Because PR39 and placental growth factor do not induce hypertrophy in cultured cardiomyocytes, coronary angiogenesis seems to be sufficient for induction of cardiomyocyte hypertrophy for labeling each cell type. In this review, we highlight recent progress in our understanding of critical roles of nonmyocytes in induction of cardiomyocyte hypertrophy.
hypertrophy. Although it is possible that superfluous supply of nutrients and oxygen associated with an increase in capillary mass might simply promote hypertrophic growth of cardiomyocytes, endothelium-derived NO is one of the critical factors that mediate angiogenesis-induced myocardial hypertrophy. NO synthase inhibitor, N(G)-nitro-L-arginine methyl ester (L-NAME), or genetic disruption of endothelial NO synthase partially prevented cardiac hypertrophy induced by PR39 or placental growth factor, although there was modest reduction in angiogenic response.7,8

Mechanistically, NO promotes proteasomal degradation of regulators of G protein signaling3 and thereby potentiates G protein–mediated hypertrophic signaling.10 Further experiments using other angiogenic factors or other endothelium-derived growth factors would be needed to argue in support of the link between angiogenesis and cardiac hypertrophy.

Endothelial Cell–Cardiomyocyte Paracrine Communications in Cardiac Hypertrophy

Endothelium-derived secreted factors participate in the functional communication with cardiomyocytes and are profoundly involved in the development of cardiomyocyte hypertrophy (Figure; Table).

ET-1 was initially identified as a potent vasoconstrictive peptide secreted from vascular endothelial cells, but is also synthesized and secreted by nonendothelial cells, such as cardiomyocytes and cardiac fibroblasts.11–13 Although both isoforms of G protein–coupled receptor for ET-1, ET(A) and ET(B) receptors, are expressed in adult cardiomyocytes, ET(A) receptors predominate and account for >80% of binding sites for ET-1.14 ET-1 is an important autocrine and paracrine regulator of cardiac hypertrophy. In cultured cardiomyocytes of neonatal rats, stimulation with ET-1 induced hypertrophic responses characterized by an increase in protein synthesis and cell size and reactivation of the fetal gene program.15 Administration of the ET(A) receptor antagonist (BQ123) attenuated cardiac hypertrophy in rats with aortic binding, indicating that ET(A) receptor plays an important role in the development of load-induced cardiac hypertrophy.15
hypertrophy. However, hypertrophic responses to angiotensin II (Ang II) or isoproterenol infusion were not attenuated in cardiomyocyte-specific ET$_A$ receptor knockout mice. Although the elevation of ET$_B$ receptor expression may compensate for the loss of ET$_A$ receptor in these mice, there is a possibility that ET$_A$ receptor in nonmyocytes, but not in cardiomyocytes, is critically involved in the development of cardiac hypertrophy. A recent study demonstrated that endothelium-derived ET-1 is not required for hypertrophic responses in pressure-overloaded hearts. Pressure overload induced functional deterioration with comparable cardiac hypertrophy in endothelial cell–specific ET-1 knockout mice. Further studies are needed to elucidate a whole picture of intercellular communications involving ET-1 in the pathogenesis of cardiac hypertrophy.

Neuregulins (NRGs) are a member of the epidermal growth factor family that plays important roles in the control of fundamental cellular responses, including cell metabolism and survival, as well as cell proliferation and differentiation. NRGs bind to the erythroblastic leukemia viral oncogene homolog (ErbB) family of receptor tyrosine kinases. In adult heart, NRG-1 and NRG-2 are synthesized and secreted by vascular endothelial cells. NRG-1 has multiple isoforms and can be divided into 3 types, type I, type II single-pass transmembrane protein, and type III 2-pass transmembrane protein. Proteolytic cleavage of type I and type III isoforms

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ANP indicates atrial natriuretic peptide; BNP, brain natriuretic peptide; cAMP, cyclic adenosine monophosphate; CTGF, connective tissue growth factor; ECM, extracellular matrix; ET-1, endothelin-1; FGF-2, fibroblast growth factor-2; IGF-1, insulin-like growth factor-1; IL-33, interleukin-33; NO, nitric oxide; NRG-1, neuregulin-1; and TGF-β1, transforming growth factor-β1.
Cardiac Fibroblasts

Cardiac Fibroblasts and Cardiac Hypertrophy

The physiological and pathological roles of cardiac fibroblasts have been studied extensively in the past decade. Cardiac fibroblasts produce the majority of extracellular matrix (ECM) proteins, such as collagens, fibronectin, laminin, and proteoglycans in the interstitium of the heart. Besides the fundamental role in fibrosis, cardiac fibroblasts participate in the development of cardiac hypertrophy (Figure; Table).

The majority of cardiac resident fibroblasts in unstressed hearts originate from epicardium. After pressure overload, endothelial cells have been reported to give rise to cardiac fibroblasts via endothelial-mesenchymal transition, and bone marrow–derived cells also seem to acquire fibroblast-like phenotypes. However, the markers frequently used to label cardiac fibroblasts, such as vimentin, periostin, thymus cell antigen 1, transcription factor 21, and fibroblast-specific protein 1 (FSP1, also known as S100A4), are not specifically expressed in cardiac fibroblasts, and these markers provide nonspecific labeling of other cell types, including endothelial or inflammatory cells.

According to a recent article using Col1al-green fluorescent protein reporter mice, 95% of cardiac fibroblasts in adult ventricular myocardium were of epicardial or endocardial origin, and none of them were of hematopoietic origin.

In response to pressure overload, cardiac fibrosis was induced by local proliferation of fibroblasts of both epicardium-derived and endocardium-derived lineages, rather than those undergoing endothelial-to-mesenchymal transition or epicardial epithelial-to-mesenchymal transition, or those of hematopoietic lineage. It remains unknown why distinct regions of myocardium are more susceptible to the development of fibrosis. For example, pressure overload or Ang II infusion induced perivascular and interstitial fibrosis, whereas epicardial and interstitial fibrosis was induced by cardiac ischemic injury.

The specific roles of cardiac resident fibroblasts might differ according to the underlying pathological processes.

Cardiac Fibroblast–Cardiomyocyte Paracrine Communications in Cardiac Hypertrophy

Cardiac fibroblasts in normal hearts and pressure-overloaded hearts have different effects on neighboring cardiomyocytes. Medium conditioned with cardiac fibroblasts isolated from pressure-overloaded rat hearts increased cardiomyocyte size, which was inhibited by transforming growth factor-β (TGF-β) type 1 receptor antagonist. These results suggest that cardiac fibroblasts and adult cardiomyocytes communicate via paracrine networks (Figure; Table).

TGF-β has pleiotropic effects and regulates the myocardial response to pressure overload. TGF-β exists in 3 isoforms, among which TGF-β1 is the predominant form. It is expressed and released by many cell types, including cardiomyocytes, cardiac fibroblasts, and immune cells. The expression of TGF-β1 in ventricular myocardium is upregulated in response to pressure overload. TGF-β1 activates SMAD-mediated signaling pathways on binding to TGF-β receptors on cardiomyocytes and cardiac fibroblasts. TGF-β1 induces transition of cardiac fibroblasts to myofibroblasts, which produces ECM proteins. TGF-β1 is an important mediator of cardiomyocyte hypertrophy downstream of Ang II stimulation, because TGF-β1 knockout mice showed blunted cardiac hypertrophy after Ang II treatment. However, a recent study demonstrated that SMAD3 knockout mice exhibited severer hypertrophy, but milder myocardial fibrosis after transverse aortic constriction (TAC).

It would be important to elucidate the roles of SMAD-dependent or SMAD-independent signaling pathways in TGF-β1–mediated hypertrophic effects.

FGF-2 also modulates the ventricular myocardial response to pressure overload. FGF-2 knockout mice exhibited a marked attenuation of cardiac hypertrophy after pressure overload induced by TAC. FGF-2 is secreted predominantly by cardiac fibroblasts and provides both paracrine and autocrine effects. In a paracrine manner, FGF-2 acts on cardiomyocytes.
and promotes hypertrophic responses in cardiomyocytes by activating the mitogen-activated protein kinase signaling.\textsuperscript{47,48} In an autocrine manner, FGF-2 activates cardiac fibroblasts to proliferate and secrete other prohypertrophic factors, such as cardiotoxin-1.\textsuperscript{43,44} Connective tissue growth factor (CTGF, also known as CCN2) also contributes to cardiac hypertrophy and fibrosis. CTGF is secreted predominantly by cardiac fibroblasts, but it is also produced by cardiomyocytes.\textsuperscript{50} CTGF acts as a cofactor for other different growth factors to promote fibrosis and wound healing by enhancing cardiac fibroblast proliferation and ECM protein deposition.\textsuperscript{51} In cultured cardiomyocytes of neonatal rats, CTGF induced cardiomyocyte hypertrophy through Akt pathway.\textsuperscript{52} Transgenic mice overexpressing CTGF did not develop cardiac hypertrophy in mice, but exhibited severer cardiac fibrosis and contractile dysfunction after pressure overload.\textsuperscript{53} However, another article reported that CTGF overexpression induced age-dependent cardiac hypertrophy and dilatation.\textsuperscript{54} The difference in the levels of transgene expression might account for the phenotypic difference, and further studies are required to elucidate the impact of CTGF on the development of cardiac hypertrophy.

Insulin-like growth factor-1 (IGF-1) regulates myocardial contractility, metabolism, growth, survival, and aging.\textsuperscript{55} In the heart, IGF-1 is produced and secreted by cardiac fibroblasts\textsuperscript{56} and promotes cardiomyocyte hypertrophy by activating IGF-1 receptor and downstream phosphoinositide 3-kinase/Akt/mammalian target of rapamycin pathway.\textsuperscript{57} Transgenic overexpression of IGF-1 receptor in the heart induced physiological hypertrophy without activation of maladaptive cardiac gene expression and fibrosis,\textsuperscript{58} and cardiomyocyte-specific IGF-1 receptor knockout mice showed blunted hypertrophic response to exercise.\textsuperscript{59} These results suggest that IGF-1 signaling promotes physiological, but not pathological hypertrophy during postnatal growth and exercise. However, administration of IGF-1 receptor antagonist exacerbated load-induced cardiac dysfunction in pressure-overloaded mice, which was accompanied by attenuation of cardiac hypertrophy,\textsuperscript{60} indicating that IGF-1 also mediates adaptive cardiac hypertrophy in response to pressure overload.

Atrial natriuretic peptide and brain natriuretic peptide are synthesized and secreted mainly by atrial and ventricular cardiomyocytes, respectively. These peptides act not only as circulating hormones but also as autocrine and paracrine mediators in the heart.\textsuperscript{61} Mechanical stretch or stimulation with humoral factors, such as ET-1 and Ang II, induced the secretion of natriuretic peptides from cardiomyocytes.\textsuperscript{62} Cardiomyocytes and cardiac fibroblasts express the natriuretic peptide receptor-A for atrial natriuretic peptide and brain natriuretic peptide.\textsuperscript{63} Systemic natriuretic peptide receptor-A knockout mice and cardiomyocyte-specific natriuretic peptide receptor-A–deficient mice exhibited enhanced cardiac hypertrophy after pressure overload induced by TAC,\textsuperscript{64,65} indicating that atrial natriuretic peptide and brain natriuretic peptide have antihypertrophic effects on cardiomyocytes. Meanwhile, both peptides show antifibrogenic effects on cardiac fibroblasts.\textsuperscript{66,67}

Adrenomedullin also exerts antihypertrophic effects by both autocrine and paracrine mechanisms.\textsuperscript{68} In response to pressure overload, adrenomedullin is synthesized and secreted by cardiomyocytes, cardiac fibroblasts, and endothelial cells. Adrenomedullin has inhibitory effects on hypertrophic growth in cardiomyocytes and also inhibitory effects on proliferation and ECM protein synthesis in cardiac fibroblasts.\textsuperscript{69–71} Adrenomedullin hetero-knockout mice showed exaggerated cardiac hypertrophy and fibrosis in response to aortic constriction.\textsuperscript{72}

Interleukin (IL)-33 also has antihypertrophic effects by a paracrine mechanism between cardiomyocytes and cardiac fibroblasts. IL-33 is predominantly produced by cardiac fibroblasts on mechanical strain\textsuperscript{73} and is also released by both cardiac fibroblasts and cardiomyocytes during cell necrosis.\textsuperscript{74} IL-33 binds to its receptor (ST2),\textsuperscript{75} whose expression in cardiomyocytes is also upregulated by mechanical strain.\textsuperscript{76} IL-33 shows antagonistic effects on cardiomyocytes against hypertrophic stimulation, such as Ang II or phenylephrine.\textsuperscript{77} The treatment of cardiac fibroblasts with IL-33 had no effect on collagen expression, although it impaired cell migration and altered the cytokine expression.\textsuperscript{78} Administration of IL-33 attenuated cardiac hypertrophy and fibrosis in pressure-overloaded mice.\textsuperscript{79}

In cardiomyocytes, stimulation of β-adrenergic receptors couples to Gs protein and activates adenylate cyclase to generate cyclic adenosine monophosphate (cAMP). Elevated intracellular cAMP activates protein kinase A, which phosphorylates downstream proteins and thereby enhances cardiac contractility.\textsuperscript{78} Stimulation of β-adrenergic receptors also induces hypertrophic growth of cardiomyocytes via both Gs/cAMP/protein kinase A and Gi/β3/γ2/Ras signaling pathways.\textsuperscript{79} A recent study demonstrated that, after β-adrenergic stimulation with isoproterenol, cAMP in cardiomyocytes was exported to outside of cells through the ATP-binding cassette transporter and worked as an extracellular signal.\textsuperscript{80} Extracellular cAMP, via its metabolite adenosine, acts on cardiomyocytes through A, adenosine receptors to inhibit cardiomyocyte hypertrophy, whereas acting on cardiac fibroblasts through A, adenosine receptors to suppress cell proliferation and ECM deposition.\textsuperscript{80} These findings indicate that cAMP serves as an extracellular autocrine and paracrine molecule, as well as intracellular signaling molecule, to regulate cardiac hypertrophy.

It has become evident that microRNAs (miRNAs) as well as proteins are involved in intercellular crosstalk between cardiomyocytes and nonmyocytes in cardiac hypertrophy.\textsuperscript{81} For instance, miR-21 in cardiac fibroblasts promoted cardiomyocyte hypertrophy by regulating the expression of growth factors, such as FGF-2, as well as ECM protein synthesis.\textsuperscript{82} In contrast, miR-29b in cardiac fibroblasts reduced ECM protein deposition, and conditioned medium of cardiac fibroblasts transfected with miR-29b decreased cell surface area of embryonic stem cell–derived cardiomyocytes, whereas that of cardiac fibroblasts transfected with miR-30c increased it.\textsuperscript{83} Other studies reported that miR-133a in cardiomyocytes downregulated the expression of fibrogenic growth factors, TGF-β and CTGF.\textsuperscript{84,85} Cardiomyocyte-specific overexpression of miR-133a in mice resulted in amelioration of cardiac fibrosis after TAC operation.\textsuperscript{86} These findings indicate that miRNAs in cardiomyocytes or cardiac fibroblasts can influence the function of neighboring cells mutually by affecting...
secretion of growth factors. In addition, miRNAs are involved in cardiac hypertrophy as paracrine molecules between cardiomyocytes and cardiac fibroblasts. A recent article has reported that miRNA-enriched exosomes are secreted by cardiac fibroblasts and taken up by cardiomyocytes. MiR-21, one of passenger strand miRNAs which are often degraded within cells, was identified by a miRNA profiling assay to be enriched in fibroblast-derived exosomes, and it was transported to cardiomyocytes, leading to cellular hypertrophy. Treatment with miR-21 antagonir led to attenuation of cardiac hypertrophy in Ang II–infused mice. These findings suggest that miRNA-enriched vesicles can mediate crosstalk between cardiac fibroblasts and cardiomyocytes during the process of cardiomyocyte hypertrophy.

Inflammatory Cells

Macrophages in the Heart
Tissue-resident macrophages play a crucial role in tissue homeostasis and pathogenesis. Recently, it has become evident that tissue macrophages, such as microglia, Kupffer cells, and Langerhans cells, originate from embryonic precursors before birth, but not from circulating monocytes after birth. In addition, tissue-resident macrophages expand their population by local proliferation rather than recruitment of circulating monocytes. A substantial portion of resident macrophages in the heart is also derived from yolk sac and embryonic progenitors which persist into adulthood. In the steady state, CCR2− macrophages constitute the major portion of cardiac macrophages and are maintained through local proliferation. However, self-renewal of embryonic-derived cardiac macrophages decline with aging, and they are replaced by monocyte-derived macrophages, even in the absence of pathological stimuli. It remains unclear whether embryonic-derived and monocyte-derived cardiac resident macrophages have distinct roles in the steady state.

Cardiac Macrophage–Cardiomyocyte Communications in Cardiac Hypertrophy
In the heart, cardiac macrophages participate in the develop-oment of cardiac hypertrophy (Figure). In the adult heart of mice, cardiac-resident macrophages constitute a heterogeneous population, with 2 distinct subsets F4/80− CD11b− Ly6c− and F4/80+ CD11b+ Ly6c+. In response to cardiac ischemic injury induced by myocardial infarction, biphatic responses of cardiac macrophages have been described. The early phase is characterized by an increase in Ly6c+ macrophages, whereas the later phase is dominated by accumulation of Ly6c− macrophages. In this case, Ly6c+ macrophages serve phagocytic, proteolytic, and proinflammatory functions, whereas Ly6c− macrophages promote tissue healing by fibroblast activation and angiogenesis. In response to pressure overload after TAC, Ly6c− cardiac macrophages are specifically increased, whereas Ly6c+ macrophages remain unchanged in number. Administration of clodronate liposome into hypertensive Ren-2 rats to deplete cardiac macrophages led to a decrease in cardiac contractile function in the early period, suggesting that cardiac macrophages are crucial for cardioprotection against pressure overload. In contrast, macrophage-specific mineralocorticoid receptor knockout mice showed blunted cardiac hypertrophy and fibrosis after aortic constriction, or administration of deoxycorticosterone/salt or L-NAME/Ang II. Macrophage-specific prolyl hydroxylase domain protein 2 knockout mice also exhibited attenuated cardiac hypertrophy, fibrosis, and contractile dysfunction after L-NAME/Ang II infusion. Furthermore, macrophage-specific miRNA-155 knockout mice showed less severe cardiac hypertrophy and contractile dysfunction after pressure overload with milder myocardial inflammation. Mechanistically, miRNA-155 promotes cardiac inflammation and hypertrophy by downregulating the expression of suppressor of cytokine signaling 1, a direct target of miRNA-155.

A recent article has demonstrated that cardiac-resident macrophages in the heart of adult mice consist of 4 distinct subsets. The macrophages in the F4/80+ CD11b+ Ly6c+ subset are further divided into major histocompatibility complex class II (MHC-II)+ CD11c+, MHC-II+ CD11c−, and MHC-II−. The other subset is F4/80− CD11b− Ly6c+ macrophage population. Ang II infusion in mice induced expansion of cardiac macrophages both through local proliferation and recruitment of circulating monocytes, and monocyte-derived macrophages gave rise to all 4 macrophage subsets. Ly6c+ MHC-II+ CD11c+ macrophages were largely CCR2+, and CCR2+ macrophages induced the production of proinflammatory cytokines, such as IL-1β, after Ang II infusion. The pathological functions of new subset of Ly6c+ macrophages during cardiac hypertrophy remain to be identified. It is also unclear how resident and newly recruited cardiac macrophages contribute to the development of pathological cardiac hypertrophy.

Cardiac T Cell–Cardiomyocyte Communications in Cardiac Hypertrophy
T cells play a central role in adaptive immunity. Although T cells are detected in the heart, their functional roles in cardiac pathophysiology are still poorly understood. It has been recently reported that both CD4+ and CD8+ T cells were increased in number in ventricular myocardium and in mediastinal heart draining lymph nodes in pressure-overloaded mice. In recombination activating gene 2 knockout mice, lack of both T and B cells prevented contractile dysfunction, but not cardiac hypertrophy, after TAC operation. The lack of CD4+ T cells in MHC-II knockout mice also prevented pressure overload–induced cardiac remodeling and failure, but the lack of CD8+ T cells did not. Meanwhile, adoptive transfer of CD4+ CD25+ regulatory T cells attenuated cardiac hypertrophy and fibrosis induced by Ang II infusion or TAC operation.

Lysyl oxidase initiates collagen crosslinking to stabilize and strengthen the collagen fibers. Recombination activating gene 2 knockout mice and MHCII knockout mice showed a significant decrease in collagen deposition after TAC operation, which was associated with a decrease in lysyl oxidase expression. Furthermore, severe combined immunodeficiency mice, in which functional T and B cells are absent, also exhibited a decrease in collagen deposition and ventricular stiffness after administration of L-NAME, which was associated with a decrease in lysyl oxidase expression. These results implicate that CD4+ T cells may stabilize collagen fibers.
through upregulation of lysyl oxidase expression in response to pressure overload, thereby contributing to cardiac fibrosis. However, mechanistic link between T cells and the development of cardiac hypertrophy remains to be elucidated.

**Cardiac Mast Cell–Cardiomyocyte Communications in Cardiac Hypertrophy**

Mast cells are involved in inflammation and tissue remodeling, as well as allergic and immune response. Mast cells reside in the heart, and the number of cardiac mast cells in the ventricle and the atrium was increased in pressure-overloaded rats and mice. The treatment of spontaneously hypertensive rats with the mast cell stabilizer resulted in suppression of cardiac fibrosis. In mast cell–deficient mice, cardiac hypertrophy and fibrosis were markedly attenuated, and contractile function was preserved after aortic constriction.

Furthermore, enhanced atrial fibrillation susceptibility after TAC operation was attenuated by administration of mast cell stabilizer cromolyn or bone marrow reconstitution from mast cell-deficient mice. Stabilizer cromolyn or bone marrow reconstitution from mast cell-deficient mice. Trypsin is synthesized and released by mast cells. Stimulation of cardiac fibroblasts with chymase induced cellular proliferation and enhanced collagen production by increasing TGF-β1 expression and SMAD activation. Myocardial chymase level was increased in pressure-overloaded rats. Treatment of ovariecetomized rats with chymase inhibitor, as well as mast cell stabilizer, ameliorated cardiac hypertrophy and fibrosis after TAC operation, and inhibited an increase in myocardial TGF-β1 expression.

Tryptase is also synthesized and released by cardiac mast cells. Myocardial tryptase level was increased in spontaneously hypertensive rats. Tryptase promoted cardiac fibroblast proliferation and collagen synthesis via activation of protease-activated receptor 2. Administration of protease-activated receptor 2 antagonist prevented cardiac fibrosis in spontaneously hypertensive rats. These findings suggest a causal relationship between cardiac mast cells and the pathological process of cardiac hypertrophy and fibrosis (Figure; Table).

**Conclusions**

In this decade, our knowledge of the role of nonmyocytes in the development of cardiac hypertrophy has been expanding. Especially, a variety of autocrine and paracrine factors are identified to mediate intercellular communications between cardiomyocytes and nonmyocytes (Table). It would be important to rank these factors according to the impact on the development of cardiac hypertrophy. The functional relevance of these factors has been investigated using the cell type–restricted gene knockout technology. We have several lines of evidence that can induce cell type–specific gene recombination. However, it will be of particular importance to clarify more precisely the lineages of nonmyocytes and to understand the specific role of subpopulations in cardiac pathophysiology. In addition, further studies are needed to elucidate the distinctive roles of nonmyocytes at the different stages from the development of cardiac hypertrophy to the transition toward heart failure.

Besides the crosstalk by humoral mediators, other modes of crosstalk may involve the intercellular communications between cardiomyocytes and nonmyocytes, such as cell–cell contacts through adhesion molecules, cell–matrix interactions, and gap junction–mediated transfer of intracellular molecules, such as ions or miRNA. Nonmyocytes function as a hub for pathophysiological responses in the heart, and further elucidation of the complex and dynamic cell–cell communications in the heart would be of great impact on the identification of new therapeutic targets for the treatment of cardiac hypertrophy and heart failure.

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**Disclosures**

None.

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