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HB-EGF Is an Essential Growth Factor for Cardiomyocyte Metabolism. The Possibility for a Novel Therapeutic Target for Heart Failure

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Because cardiomyocytes lose the capability of proliferation since the early embryonic stages, the adaptations for various insults are mainly mediated by their morphological and metabolic changes. However, how cardiomyocytes response to these stimuli and maintain their function still remains unknown. Here we show the evidence that HB-EGF (heparin binding EGF like growth factor) is a key molecule to transmit the important signals to maintain the function of cardiomyocytes. Previously, we have shown that HB-EGF, not like other EGF family ligands, is a specific mediator of signal transduction following the stimulation of G protein coupled receptors(GPCR) due to agonists such as cathecholamine, angiotensin II or endothelin I. Blockade of the shedding of HB-EGF from cellular membrane by a metalloproteinase inhibitor attenuated cardiac hypertrophy caused by these GPCR agonists. These data imply that generation of cardiac hypertrophy is one of functions of HB-EGF. On the other hand, we newly generated the mouse in which the HB-EGF function was moderated, and found that HB-EGF is an essential factor to maintain cardiac metabolism and the lack of HB-EGF function causes cardiac cellular death, causing the phenotype similar to human dilated cardiomyopathy. These phenotypes resembled to that of HER2 (One of the EGF receptor family) heart specific deficient mice, and HB-EGF can phosphorylate HER2 of cardiomyocytes, both suggesting that HER2 phosphorylation by HB-EGF is an essential signal transduction to maintain its function. These data strongly imply that HB-EGF or its signaling molecule is involved in the pathophysiology of heart failure and these molecules may become potential therapeutic targets for chronic heart failure.

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Kruppel-Like Zinc-Finger Transcription Factor KLF5/BTEB2 Is a Target for Angiotensin II Signaling and an Essential Regulator of Cardiovascular Remodeling.

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In response to metabolic and mechanical stress, the heart and vasculature undergo structural remodeling which underlie the pathogenesis of heart failure and atherosclerosis. Locally expressed growth factors are known to play key roles in these processes; however, their transcriptional regulation remains poorly understood. We recently isolated a Kruppel-like zinc-finger transcription factor, KLF5/BTEB2, which is markedly induced in activated cells of mesenchymal origin. We clarified in vivo function of KLF5 using KLF5 knockout mice (KLF5 +/-). We performed vascular injury model using a polyethylene tube cuff placed around the femoral artery. The arteries of the KLF5 +/- were thin-walled and dilated, which was in striking contrast to the wild-type animals, which showed thickened medial and intimal layers. KLF5 +/- also showed impaired angiogenic activity in a hindlimb ischemia model, in which the femoral arteries were ablated, and angiogenic responses to implanted tumors were markedly attenuated. Following continuous infusion of angiotensin II, the hearts of wild-type mice were significantly heavier than those of KLF5 +/- and showed much more prominent perivascular and interstitial fibrosis. In addition, we found that angiotensin II induces expression of KLF5 which, in turn, activates PDGF-A and TGF β expression. Finally, we identified novel interaction between KLF5 and retinoic acid receptor (RAR) and showed that synthetic RAR ligands are able to modulate transcriptional activity of KLF5. Furthermore, in vivo administration of RAR ligands affects stress responses in the cardiovascular system in a KLF5-dependent manner. KLF5 thus appears to be a key element linking external stress and cardiovascular remodeling.

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Critical Roles of Fas/Fas Ligand Interaction and Beneficial Effect of Soluble Fas Gene Therapy for Post-Infarct Ventricular Remodeling and Dysfunction

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Patients suffered from large myocardial infarction (MI) have a high risk for the development of chronic heart failure. Myocardial infarct transits from acute myocyte death and acute inflammatory cell infiltration (acute stage) to cell-rich granulation tissue containing, as chief components, neovasculature and myofibroblasts that synthesize collagen and have contractile elements (subacute stage). However, these cells disappear during the natural course via apoptotic mechanism to complete a final scarring with scanty cells (chronic stage). In the present study, we have found augmented expression of both Fas and Fas ligand in the granulation tissue cells at the subacute stage of MI; this suggested the apoptosis was Fas-induced. Next, apoptotic rate of the granulation tissue cells was significantly fewer in mice lacking functioning Fas (lpr/lpr strain) and in those lacking Fas ligand (gld/gld strain) compared with that of control mice (C57BL/6J), and post-infarct ventricular remodeling and dysfunction were greatly attenuated in these strains. Finally, we examined therapeutic effects of blocking the Fas/Fas ligand interaction using exogenous soluble Fas (sFas) on post-infarct left ventricular remodeling and heart failure. Mice were transfected with adenovirus encoding sFas on the 3rd day of MI. The treatment with sFas gene successfully suppressed apoptosis of granulation tissue cells, resulting in a thick infarct wall with rich cell components at chronic stage (4 weeks later) in which vessels, myofibroblasts and mature smooth muscle cells with contractile phenotype were abundant among fibrous tissue. The treatment greatly alleviated post-infarct left ventricular remodeling and dysfunction. Our new therapeutic concept may become one breakthrough in the management of chronic heart failure after large MI.

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Role of Proinflammatory Cytokines in Cardiac Remodeling

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Myocardial production of proinflammatory cytokines, especially tumor necrosis factor (TNF)- α, are increased in patients with congestive heart failure. To investigate the role of proinflammatory cytokines in myocardium, we made transgenic mice with cardiac-specific overexpression of TNF- α (TG). These mice developed myocardial inflammation with progressive ventricular hypertrophy and dilatation, suggesting that TNF- α may play an important role in the pathogenesis of cardiac remodeling. TNF- α increased activity of inducible nitric oxide synthase (iNOS) and matrix metalloproteinases (MMP) in myocardium. Apoptosis was also increased; however, this was largely isolated to the interstitial cells. To evaluate therapeutic effects of anti-TNF treatment on these mice, an adenovirus encoding an extracellular domain of human 55-kDa TNF receptor (AdTNFRI) was injected. AdTNFRI significantly abrogated myocardial inflammation and restored down-regulation of α-myosin heavy chain and sarcoplasmic reticulum Ca^{2+}-ATPase promptly. We then investigated the significance of iNOS and MMP activation in cytokine-induced cardiac remodeling. Crossing TG mice with iNOS knockout mice abolished the iNOS activity and significantly improved β-adrenergic inotropic responsiveness; however, it did not prevent cardiac remodeling or improve the survival. In contrast, treatment with an MMP inhibitor BB-94 significantly reduced ventricular fibrosis and hypertrophy, and prolonged the survival of TG mice. These results indicate that activation of MMP but not iNOS may play a pivotal role in the pathogenesis of cardiac remodeling. TNF- α transgenic mice may provide a unique model in which to study myocardial inflammation and remodeling and to explore novel therapeutic strategies for congestive heart failure.

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Mammalian Target of Rapamycin (mTOR): A New Molecular Target for Cardiac Hypertrophy

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Background: Rapamycin, a lipophilic macrolide, has been used as an immunosuppressant in clinical practice. Recently, it is shown that rapamycin-coated stents effectively prevent restenosis after coronary angioplasty. The