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Review Article

Role of hepatocyte growth factor in heart failure: from therapeutic potential to prognosis assessment

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CONTENTS

Abstract

Hepatocyte growth factor (HGF) is a mesenchymally derived heterodimeric glycoprotein that was first recognized as a stimulator of hepatocyte proliferation. It is now known that HGF, as a multipotent cytokine, plays a role in mitogenesis, angiogenesis, morphogenesis, tumor metastasis, cell motility and cell growth via activation of the transmembrane tyrosine kinase receptor c-Met. This review focuses on the effects of HGF on heart failure of different etiopathogenesis, emphasizes the multiple mechanisms that underlie the beneficial effects of HGF, and discusses its value for assessing prognosis in heart failure.

Introduction

Hepatocyte growth factor (HGF, also known as scatter factor) was first identified in 1984 (1, 2) and 1985 (3) and purified as a potent mitogen from cultured primary hepatocytes (4). Molecular cloning revealed that it is a heterodimeric molecule composed of a 69-kD α-chain and a 34-kD β-chain. The α-chain contains an *N*-terminal hairpin domain and four kringle domains, wheras the β-chain contains a serine protease-like domain with no enzymatic activity (5, 6). As a multipotent cytokine, HGF plays a role in mitogenesis, angiogenesis, morphogenesis, tumor metastasis, cell motility and cell growth via activation of a transmembrane tyrosine kinase receptor known as c-Met. Because of its potential angiogenic, antiapoptotic, antifibrotic and stem cell-recruiting effects, HGF has been the subject of increasing attention in cardiovascular diseases (7-9).

Heart failure may be the only cardiovascular disease for which the incidence and prevalence rates are increasing. Despite advances in medical and surgical treatment of this syndrome, the prognosis for heart failure patients remains grim (10, 11). Therefore, new therapeutic strategies are needed. The present review focuses on the potential therapeutic role of HGF in heart failure. We also assess the findings on the application of HGF to treat heart failure of different etiopathogenesis in animal models, emphasize the multiple mechanisms that underlie the beneficial effects of HGF and discuss its value for assessing prognosis in heart failure.

Beneficial effects of HGF in treating heart failure

The syndrome of heart failure can be produced by many diseases, mainly coronary artery disease with resulting myocardial infarction (MI) or loss of functioning myocardium (ischemic cardiomyopathy), hereditary cardiomyopathy, systemic hypertension, etc. These diseases lead to the development of pathological processes, including massive myocyte cell dropout and/or cardiocyte apoptosis, fibrosis and ventricular remodeling, finally leading to heart failure.

Postinfarction heart failure

HGF gene therapy is considered to be a potential therapeutic strategy for patients with postinfarction heart failure. However, in the clinic such patients mostly have a chronic course and unchanging infarct size. Therefore, preclinical studies for the attenuation of postinfarction heart failure should be designed to test the effect of intervention on ventricular remodeling and cardiac function, independent of the direct effect on infarct size. Ideally, the intervention should be initiated at least 1 day after postmyocardial infarction, as ischemia–reperfusion injury and infarct size are largely determined during the initial 24 h after infarct.

Jayasankar et al. (7) demonstrated that postinfarction HGF gene therapy decreases adverse ventricular remodeling and improves cardiac function in a mouse model. A replication-deficient adenovirus (Ad) encoding HGF or a control null virus was directly injected into myocardium the third week after ligation of the left anterior descending coronary artery. Three weeks after injection, Ad-HGF-treated animals had greater preservation of maximum left ventricular (LV) pressure, maximum dP/dt and LV border zone wall thickness than null virus-treated groups. The authors suggested that these beneficial effects from HGF gene therapy were associated with an enhancement in angiogenesis and a reduction in apoptosis.

Consistent with the beneficial effects on LV remodeling and function in response to local intramyocardial transfection of the HGF gene in the mouse model of postinfarction heart failure, a study by Wang et al. (12) demonstrated that systemic HGF gene transfer attenuates postinfarction heart failure in a mouse model of MI. On day 1 after MI, HGF (0.45 mg/kg/day) or sodium chloride was injected into the tail vein for 7 days. Compared with control sodium chloride treatment, HGF gene treatment for 4 weeks improved cardiac contractility, significantly preserved LV geometry, attenuated LV dilatation and normalized LV free wall thickness. Moreover, the treatment led to an increase in endothelial cells and a reduction in apoptosis and fibrosis. These findings indicate that postinfarction treatment with the HGF gene greatly reduces chronic LV remodeling and dysfunction, likely by inducing hypertrophy of cardiomyocytes, increasing infarct wall thickening, preserving vessels, inhibiting apoptosis and reducing fibrosis. In this study, a striking finding was that c-Met- and c-kit-positive "cardiomyocytes" were observed in the border area and epicardium. However, we could not find evidence to certify that these cells were "mature cardiomyocytes".

In 2003, Beltrami et al. (13) discovered the existence of $Lin^-/c\text{-}kit^+$ cells with the properties of cardiac stem cells in rats. These cells are self-renewing, clonogenic and multipotent, giving rise to myocytes, smooth muscle cells and endothelial cells. When injected into an ischemic heart, these cells or their clonal progeny reconstitute well-differentiated myocardium, formed by new blood-carrying vessels and myocytes with the characteristics of young cells, encompassing approximately 70% of the ventricle. However, the identification marker of cardiac stem cells may vary in different species, as $c\text{-}kit^+$ cells represent a population of stem cells of nearly all lineages (14).

Similar to Wang et al., in a recent study (15) we demonstrated that HGF can improve the number of $c\text{-}kit^+/c\text{-}Met^+$ cells in ischemic myocardium in a postinfarction swine model. In comparison with the mock virus group, the number of $c\text{-}kit^+$ cells co-expressing c-Met was significantly higher in the Ad5-mediated human HGF (Ad5-hHGF) gene therapy group. These $c\text{-}kit^+/c\text{-}Met^+$ cells were possibly cardiac stem cells, which could be recruited and/or mobilized by HGF. The mechanism of the beneficial effect of HGF on postinfarction heart failure may not be limited to stimulation of angiogenesis and inhibition of apoptosis and fibrosis, but may also involve the recruitment of stem cells into the myocardium.

Cardiomyopathic heart failure

To determine the effects of HGF on ischemic cardiomyopathy, Azuma et al. (16) injected human HGF plasmid DNA into ischemic myocardium in a porcine model. One month after injection, the ischemic area was significantly reduced in the HGF group, accompanied by a significant increase in capillary density and regional myocardial perfusion in the ischemic area. In contrast, the fibrotic area was decreased significantly in the HGF group, which was associated with a significant decrease in collagen I, III and transforming growth factor β (TGF-β) synthesis compared to the control group. Consistently, cardiac function was significantly improved in the 4 mg HGF group compared to the control group. Overall, this in vivo experiment demonstrated that intramyocardial injection of human HGF plasmid DNA in ischemic cardiomyopathy resulted in a significant improvement in cardiac function via an increase in blood flow and a decrease in fibrosis. These favorable outcomes suggest potential utility for HGF gene transfer in the treatment of patients with ischemic heart disease. Moreover, a phase I study in our center using Ad5-hHGF validated this concept (17).

Hereditary cardiomyopathy also seems to respond positively to HGF gene therapy. Using cardiomyopathic Syrian hamsters with a genetic defect in δ-sarcoglycan, Nakamura et al. (18) investigated the potential involvement of HGF in the pathophysiology and therapy of dilated cardiomyopathy, because HGF has previously been shown to be cytoprotective and to have benefits in acute heart injury. Late-stage TO-2 cardiomyopathic hamsters showed severe cardiac dysfunction and fibrosis, accompanied by increases in myocardial expression of TGF-β1, a growth factor responsible for tissue fibrosis. Conversely, HGF was downregulated in late-stage myopathic hearts. Treatment with recombinant human HGF for 3 weeks suppressed cardiac fibrosis, accompanied by decreased expression of TGF-β1 and type I collagen. Suppression of TGF-β1 and type I collagen by HGF was also demonstrated in cultured cardiac myofibroblasts. Likewise, HGF suppressed myocardial hypertrophy, apoptosis in cardiomyocytes and the expression of atrial natriuretic peptide (ANP), a molecular marker of hypertrophy. Importantly, downregulation of fibrogenic and hypertrophic genes by HGF treatment was associated with improved cardiac function. Thus, a decrease in endogenous HGF levels may participate in the susceptibility of cardiac tissue to hypertrophy and fibrosis, and exogenous HGF led to therapeutic benefits in dilated cardiomyopathy in this model, even with late-stage treatment.

Consistent with the beneficial effects of HGF gene transfer in the above-mentioned experiments, a study by Ahmet et al. (19) demonstrated that myocardial HGF gene transfer attenuated rapid-pacing-induced cardiomyopathic heart failure in a canine model. Four weeks after gene transfection, LV global function was improved in the

HGF group as preload-recruitable stroke work, whereas it was not changed in the control group. Weekly echocardiography showed that this improvement began during the week after gene transfer. The hearts in the HGF group had a large wall thickness, large myocyte diameter, high capillary density, low fibrotic area fraction and low density of apoptotic nuclei compared with the control group, as seen on histological analysis. Myocardial perfusion flow was increased in the HGF group, whereas it was reduced in the control group. Overall, HGF gene transfection stimulated angiogenesis, improved perfusion, decreased fibrosis and apoptosis, promoted recovery from myocyte atrophy, and thereby attenuated cardiac remodeling and improved myocardial function in the failing heart. It is therefore a novel gene therapy for cardiomyopathic heart failure.

Hypertensive heart failure

Recently, Sakaguchi et al. showed for the first time that HGF gene therapy decreases adverse ventricular remodeling and improves cardiac function and survival in spontaneously hypertensive rats (SHR) (20). The authors developed an HGF-incorporating gelatin hydrogel sheet (HGF sheet), which was designed to release HGF for more than 2 weeks in vivo. Stroke-prone SHR at 25 weeks of age received placement of an HGF sheet on the left ventricular free wall or sham operation. After 4 weeks, fractional shortening was significantly higher and left ventricular diastolic dimension was significantly smaller in the HGF group than in the control group. The slope of the peak early diastolic filling velocity and the ratio of that slope to the slope of the peak filling velocity at atrial contraction were significantly lower in the HGF group than in the control group. Myocardial fibrosis was reduced and capillary density was significantly greater in the HGF group than in the control group. The survival rate at 10 weeks after surgery was much higher in the HGF group than in the control group. These findings indicate that the treatment of hypertension with HGF gene therapy greatly reduces chronic LV remodeling and dysfunction, likely by inducing angiogenesis and reducing fibrosis.

Mechanisms underlying the beneficial effects of HGF in heart failure

The mechanisms underlying the beneficial effects of HGF treatment on heart failure are quite complex (Fig. 1).

Angiogenesis/arteriogenesis

The angiogenic properties of HGF may depend on upregulation of an essential transcription factor for angiogenesis, ets-1. HGF may upregulate the transcription activity and mRNA expression of ets-1. Moreover, ets-1 may activate HGF, matrix metalloproteinase MMP-1, c-Met and vascular endothelial growth factor (VEGF) expression in vascular smooth muscle cells and endothelial cells, which in turn upregulate the degradation pathway of the extracellular matrix and stimulate the migration of vascular smooth muscle cells and endothelial cells, leading to angiogenesis (21).

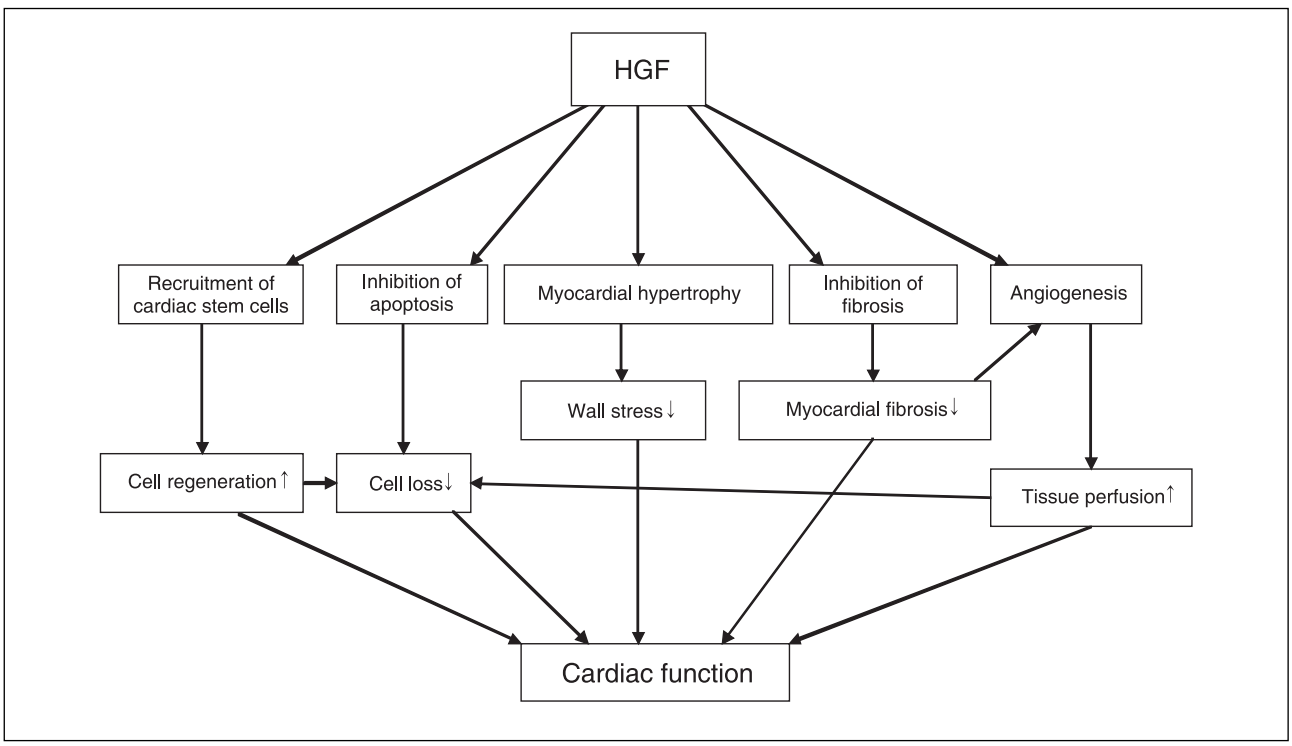

Fig. 1. The mechanisms underlying the beneficial effects of HGF treatment on heart failure.

Vasculogenesis refers to the formation of blood vessels from endothelial progenitor cells, a process that was initially described as occurring during embryonic development, and more recently, also in adult animals. Angiogenesis involves the sprouting of new capillaries from pre-existing vessels, whereas arteriogenesis refers to the remodeling of newly formed or pre-existing vascular channels into larger and well-muscularized arterioles and collateral vessels. The generation of new vascular channels by vasculogenesis and angiogenesis leads to arteriogenesis, involving coating with smooth muscle cells, followed by the formation of mature blood vessels. Recruitment of smooth muscle cells provides these vessels with essential viscoelastic and vasomotor properties and enables accommodation of the changing needs for tissue perfusion. This stage has a major role in collateral growth (22, 23). In prior studies on neovascularization, factor VIII (von Willebrand factor) has been commonly used to evaluate the degree of neovascularization (7, 16, 24), but this method cannot distinguish between perfusion vessels and nonperfusion vessels. Therefore, an increase in the number of vessels as indicated by this method might not necessarily indicate an improvement in perfusion function. In contrast to other studies, we discovered that HGF can increase not only the factor VIII-marked vessels, but also the number of functional perfusion arterioles surrounded by α-smooth muscle actin (α-SMA), which improves cardiac perfusion and thus preserves cardiac function (25).

Inhibition of apoptosis

Apoptotic myocyte cell death is an independent and crucial contributor to ventricular remodeling in heart failure of different etiologies, including myocardial ischemia and infarction. After MI, ventricular wall thinning occurs not only in the infarcted necrotic zone but also in the border zone region. The interaction of the infarcted area with the remaining viable myocardium results in supraphysiological stretch across the border zone, which increases the tension load or wall tension, causing the ventricle to remodel and dilate. The increase in wall tension, the reduction in wall thickness and further ventricular dilatation may involve mural translocation of cells, a phenomenon known as side-to-side slippage of myocytes. Lateral slippage of myocytes appears to be an early event that may accelerate dilated cardiomyopathy after acute MI (26, 27), and cell loss may result in slippage of the remaining myocytes (27, 28). Apoptosis may play a role in the cell loss. It is noteworthy in this regard that inhibition of apoptosis by the antiapoptotic factor Bcl-2 protects against chronic postischemic heart failure (27). HGF is also a potent antiapoptotic factor, and recent work demonstrates that HGF protects cardiomyoctes from apoptosis via a signaling pathway involving MEK/ERK-dependent phosphorylation of GATA-4 (29). HGF gene transfer attenuates postinfarction heart failure, which is associated with a significant reduction of myocardial apoptosis that correlates with increased Bcl-2 and Bcl-xL expression. It is believed that blocking the activation of apoptosis after myocardial injury prevents cell loss and preserves myocardial geometry and function (30). It should be noted, however, that the role of cardiomyocyte apoptosis in the pathogenesis of MI and heart failure is under debate mainly due to problems with detection methods and quantification (31-35). There is no doubt that the apoptotic cascade is activated in both ischemic and heart failure conditions, but the true importance of apoptosis as a contributor to disease progression remains to be determined (33). Therefore, further studies are needed to confirm the role of inhibition of apoptosis as a therapeutic mechanism of HGF in MI and heart failure.

Mobilization/recruitment of "cardiac" stem cells

In 2004, it was found that mouse postnatal bone marrow contains potential cardiac progenitors that could be chemoattracted to the infarcted myocardium in an HGF/c-Met-dependent manner that is similar to SDF-1/CXCR4 and LIF/LIF-R (36). Based on this, we applied adenosvirus-mediated human HGF gene therapy intracoronarily to the infarcted area in pigs to analyze the recruitment of c-kit$^+$ stem cells and the improvement in heart failure (15). The reason that we chose c-kit$^+$ as the identification marker of "cardiac" stem cells was (as mentioned above) that the expression of other markers may vary in different species, whereas c-kit$^+$ cells represent a population of stem cells of nearly all lineages (14). We found that HGF improves the recruitment of c-kit$^+$/c-Met$^+$ stem cells into ischemic myocardium. Moreover, these cells aggregate to nidi in the perivascular myocardium (15). In another study, patients with extensive coronary heart disease were treated with intracoronary infusion of the HGF gene plus stent implantation or physiological saline plus stent implantation, The number of circulating CD34$^+$ cells in the HGF gene treatment group at 6 h after the procedure and the number of circulating c-kit$^+$ cells at 6 days after the procedure were significantly higher than in the control group (37). These findings demonstrate that the administration of the HGF gene could mobilize and/or recruit "cardiac" stem cells. Further studies should examine whether the "cardiac" stem cells mobilized/recruited by HGF are able to transdifferentiate to cardiac muscle cells through the induction of HGF in vivo (38, 39).

Myocardial hypertrophy

HGF gene therapy postinfarction results in substantial cardiomyocte hypertrophy at the edges of the infarcted tissue (including papillary muscle and trabeculae), accompanied by overexpression of c-Met, a transmembrane tyrosine kinase through which HGF activates the Ras/Raf/MEK/ERK signaling pathway, thus contributing to myocardial hypertrophy (19). The significant HGF-induced thickening of the infarcted wall may prevent the vicious circle of postinfarct ventricular remodeling, as wall stress that accelerates ventricular dilatation is more markedly increased in the thinner wall according to Laplace's law (40). Although pathological cardiomyocyte

hypertrophy usually further aggravates cardiac function, this type of cardiomyocyte hypertrophy induced by HGF is associated with increasing blood supply and may therefore lead to a better result from treatment. Further long-term follow-up studies should focus on cardiomyocyte hypertrophy induced by HGF.

Inhibition of fibrosis

In the chronic phase of MI, the progression of cardiac remodeling with reduced cardiac function leads to interstitial fibrosis and damage to cardiomyocytes. In particular, fibrosis in the noninfarcted area may be one of the major causes of ventricular remodeling in ischemic cardiomyopathy (41). HGF exerts a potent antifibrotic effect, which may be related to activation of matrix metalloproteinases, inhibition of collagen formation and inhibition of TGF activated by angiotensin II (19, 42). HGF gene therapy has been shown to reduce myocardial fibrosis in a mouse model of postinfarction heart failure (40), a canine model of cardiomyopathy and heart failure (19), and a hamster model of chronic cardiomyopathy (43). The HGF-induced reduction of myocardial fibrosis is believed to be beneficial in improving contractile function and angiogenesis in the failing heart (19, 40).

Assessing prognosis in heart failure

Assessing the prognosis of an individual patient with heart failure is difficult. Traditional tools available to physicians include physical examination, invasively measured hemodynamics, echocardiography and exercise capacity. Combining a host of risk factors into a single heart failure survival score has been suggested. More recently, the powerful prognostic value of B-type natriuretic peptide (BNP) levels has been demonstrated (44), and incorporation of biomarkers into the risk assessment of patients with heart failure has become an area of considerable interest. Following on the momentum of BNP and other neurohormones to assess risk in chronic heart failure (CHF), *N*-terminal proBNP, cardiac troponins, endothelin-1 (ET-1), cystatin C and C-reactive protein (CRP) have emerged as potentially useful candidate biomarkers in this setting (45-49).

Lamblin et al. (50) investigated the prognostic value of two cytokines, VEGF and HGF, in 529 patients evaluated for reduced LV ejection fraction. VEGF was shown to have limited prognostic utility, as has been demonstrated by others (51). However, increased levels of HGF were strongly associated with markers of congestive heart failure (CHF) severity, such as higher New York Heart Association (NYHA) class and lower LV ejection fraction, as well as clinical outcomes including both cardiac and overall mortality. The association of HGF with adverse outcomes persisted in multivariate analysis that incorporated state-of-the-art risk factors such as BNP and peak oxygen consumption, an important step when assessing a new biological marker. It appears that HGF may influence the natural history of CHF via an effect on the remodeling process (52, 53). HGF may be an attractive biomarker in patients with CHF because it is increased in the setting of cardiomyocyte apoptosis and active remodeling, thereby identifying individuals who are at increased risk of adverse clinical outcomes. However, the multi-biomarker approach is thought to be beneficial because each marker identifies a different component of the pathophysiology of this disease —myocardial necrosis by troponin I, inflammation by CRP and left ventricular overload by BNP. A marker of cellular apoptosis and hence cardiac remodeling, such as HGF, may be an ideal candidate to add complementary predictive power in assessing heart failure prognosis. From a mechanistic standpoint, further work is needed to clarify the link between HGF and the remodeling process and apoptosis. Endomyocardial biopsy specimens, myocardial tissue explanted at the time of transplantation and gadolinium-enhanced cardiac magnetic resonance imaging (MRI), including serial imaging studies, are potential resources that may help to better define the relationship of HGF levels with apoptosis, ventricular scar and subsequent ventricular enlargement.

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