Review

Hepatocyte Growth Factor (HGF) as a Potential Index of Severity of Hypertension

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Hepatocyte Growth Factor (HGF) is a mesenchyme-derived pleiotropic factor that regulates cell growth, cell motility, and morphogenesis of various cells, and is thus considered a humoral mediator of epithelial-mesenchymal interactions. We previously identified HGF as a novel member of the family of endothelium-specific growth factors. Moreover, the presence of a local HGF system (HGF and its specific receptor, c-met) has been demonstrated in vascular cells both in vitro and in vivo. HGF might contribute to the protection and/or repair of vascular endothelial cells injured by high blood pressure. If so, serum HGF level might be elevated in response to endothelial cell damage. To test this hypothesis, we measured serum levels of HGF in hypertensive and normotensive patients. Serum HGF concentration in hypertensive patients without any complications was significantly higher than that in normal subjects. Interestingly, serum HGF concentration in hypertensive patients with complications was significantly higher than that in either hypertensive patients without complications or normotensive subjects. Of importance, hypertensive patients treated with antihypertensive drugs showed the same level of serum HGF concentration as normotensive subjects. In contrast, serum HGF concentration in diabetic patients without hypertension was significantly lower than that in normal subjects, whereas serum HGF concentration in diabetic patients with hypertension was significantly higher than that in normal subjects. Moreover, serum HGF concentration in diabetic patients with hypertension complications was even higher than that in diabetics without complications. This review discusses the possibility that HGF may be considered as a new index of the severity of hypertension. (Hypertens Res 1999; 22: 161-167)

Key Words: endothelium, endothelial dysfunction, vascular remodeling, hypertension, atherosclerosis

The concept of the local control of both vascular tone and structure by locally synthesized growth factors has recently been described (1). These local systems appear to be independently regulated by regional factors and may play important physiologic and pathophysiologic roles. On the other hand, endothelial cells are also known to secrete various vasoactive substances and may modulate vascular growth via the secretion of nitric oxide (NO), vascular natriuretic peptides, and many other antiproliferative factors. Thus, numerous endothelium-derived substances (prostaglandin I2 (PGI2), NO, C-type natriuretic peptide (CNP)) also have profound influences on vascular smooth muscle function (2). Indeed, co-culturing of endothelial cells with vascular smooth muscle cells (VSMC) has been shown to significantly decrease DNA synthesis of VSMC (3). On the other hand, it is apparent that dysfunction of endothelial cells may promote abnormal vascular growth, such as that in atherosclerosis. For these reason, vascular remodeling plays an important role in the pathophysiology of atherosclerosis, restenosis and hypertension. It is becoming increasingly apparent that, among the many factors that may influence vascular structure, vasoactive substances are likely to play a major role.

From this viewpoint, hepatocyte growth factor (HGF) has received perhaps the most attention as a candidate vasoactive substances. Although HGF is known to stimulate hepatocyte growth (4-16) (Fig. 1), recent findings suggest that HGF also stimulates epithelial and various other cells (7-9). HGF is a mesenchyme-derived pleiotropic factor that regulates cell growth, cell motility, and morphogenesis of various types of cells, and is thus considered a humoral mediator of the epithelial-mesenchymal interactions that in turn control morphogenic tissue interactions during embryonic development and organogenesis (10, 11).

HGF as Endothelium-Specific Growth Factor

In our previous study, and in those of other authors, HGF was shown to stimulate DNA synthesis and growth of endothelial cells in a dose-dependent manner, much like fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF) (3, 12, 13), although the stimulation of endothelial cell growth by HGF was more potent than that by these other two factors (3, 12, 14). In VSMC, however,

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neither HGF nor VEGF stimulated DNA synthesis, while the addition of exogenous bFGF resulted in a significant increase in DNA synthesis. Thus, both HGF and VEGF secreted from VSMC show the characteristics of endothelium-specific growth factors acting on endothelial cells (15), 16).

Regarding the potential physiological role of the local HGF system, it is of interest that HGF abrogates the decrease in DNA synthesis and cell death of endothelial cells induced by serum-free treatment (17), an inducer of endothelial apoptosis (18). HGF should therefore be classified as a new member of the family of growth factors showing anti-cell death activities. More importantly, our previous study demonstrated that HGF attenuated the apoptotic, aortic endothelial cell death induced by high D-glucose (19). In addition, HGF has been reported to demonstrate anti-apoptotic activity against endothelial and epithelial cell death induced by such stimuli as TNF-α treatment (20, 21). The mechanisms by which HGF prevents the cell death induced by these conditions remain unclear. HGF is known to stimulate phosphatidylinositol-3'-kinase (PI3K), protein tyrosine phosphatase 2, phospholipase C-γ, pp60-src and grb2/hSos1 (22-25). Moreover, HGF stimulates the rho- and ras-mediated signal transduction pathways, resulting in an increase in actin fibers (26, 27). Its activation of these signal transduction pathways suggests that HGF will act to prevent cell death.

Presence of Local HGF System in Cardiovascular Organs

Many growth factors have been postulated to work as local vascular modulators in an autocrine-paracrine manner. It is well known that HGF is synthesized in large amounts in the liver and secreted into the blood (4, 28). However, HGF transcripts and immunoreactive peptides are also found in numerous locations, including the kidney and lung (29-32). Moreover, the specific receptor of HGF, c-met, has been shown to be expressed in many target organs, including the brain and kidney (29, 30). This has led to the speculation that locally synthesized HGF may influence local functions. HGF mRNA was detected in aortic endothelial cells and VSMC by RT-PCR (29), and c-met RNA has been detected in endothelial cells and VSMC. In this context, it is of importance that the existence of a local HGF system (HGF and c-met) was also confirmed in human and rat aortas in vivo (29).

In addition to the in vitro evidence, HGF mRNA has been readily detected in the heart, kidney and blood vessels of Wistar-Kyoto rats (WKY) and spontaneously hypertensive rats (SHR) in vivo (30). Interestingly, SHR showed lower renal, cardiac, and vascular HGF concentrations than WKY at the age of 25 wk, at which time these organs in SHR revealed hypertrophic changes due to hypertension (30). Cardiac HGF concentration also showed a significant negative correlation with left ventricular (LV) mass, accompanied by decreased cardiac HGF mRNA. The decreased local HGF production demonstrated in blood vessels and the heart in SHR may be related to the development of cardiovascular hypertrophy. If production of local HGF, an endothelial protectant, were decreased, dysfunction of endothelial cells might be accelerated. Moreover, it has been well established that hypertension decreases the number of capillary vessels in the heart. Importantly, a recent study revealed the angiogenic property of HGF in a rabbit hindlimb model (32). Therefore, decreased local HGF production in the heart may also be related to cardiac remodeling induced by hypertension.

Because the local HGF and VEGF systems are expected to play a role in the pathogenesis of cardiovascular disease, the interaction between the HGF system and either TGF-β or angiotensin II, both of which are known to be increased in atherosclerotic and restenotic lesions after angioplasty (33-35) might be of importance. A marked reduction of local HGF production by TGF-β and Ang II treatment has been observed in endothelial cells, VSMC and mesangial cells (20, 30, 31). The promoter region of the HGF gene contains various binding sites for transcription factors, e.g., interleukin 6 response elements, binding sites for nuclear factor interleukin 6 (NF-IL 6), a TGF-β inhibitory element, and a camp responsive element (36). Probably, TGF-β inhibits HGF production through a TGF-β inhibitory element at the transcriptional level. On the other hand, exogenous addition of recombinant rat HGF has been shown to stimulate local human HGF release into culture medium in both human endothelial cells and human VSMC (37). This phenomenon raises the interesting hypothesis that HGF itself may regulate local HGF production by autoloop-positive feedback, and may work in an autocrine-paracrine manner (Fig. 2). The break of this autocrine-loop, which maintains endothelial cell growth, by TGF-β and Ang II may result in abnormal growth of VSMC and cardiac myocytes. Importantly, blockade of the angiotensin
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system by administration of an ACE inhibitor or Ang II receptor antagonist increases cardiac and vascular HGF in accordance with the improvement of left ventricular hypertrophy and vascular hyper trophy (30).

Suppression of local HGF production also occurs under more physiological conditions. Local HGF production in endothelial cells and VSMC was markedly suppressed by high D-glucose, probably due to increased TGF-β concentration (19). These results suggest that decreased local HGF production may promote the progression of arteriosclerotic vascular changes in diabetes mellitus. Prostaglandin (PG) E₁, PG₁₂ analogue and cilostazol, which are well known to improve peripheral arterial disease in patients with diabetes mellitus (DM), attenuated endothelial cell death induced by high D-glucose through the stimulation of local HGF production (17). Increased vascular HGF production by these agents may contribute to the efficacies of PG₁₂ analogue and cilostazol in the treatment of such peripheral arterial diseases as arteriosclerosis obliterans (ASO), which is observed in DM, although further studies on this subject will be needed. The regulation of local HGF production in cardiovascular cells is summarized in Fig. 3.

HGF Is a Potential Index of Severity of Hypertension

HGF is suggested to play an important role in tissue regeneration (9–11), and systemic HGF may act as a humoral mediator in tissue regeneration, in addition to autocrine-paracrine local HGF production. Serum HGF concentration has been reported to be elevated in response to organ damage, such as in hepatitis and nephritis (38–40). We therefore evaluated the relationship between circulating HGF and blood pressure in normotensive and hypertensive patients. Based on the in vitro data and the results of our evaluation, it was hypothesized that HGF might contribute to the protection or repair of vascular endothelial cells. If so, serum HGF level might be elevated in response to endothelial cell damage induced by hypertension (Fig. 4). And indeed, serum HGF level might be elevated in response to endothelial cell damage induced by hypertension (Fig. 4). And indeed, serum HGF concentration has been shown to be markedly increased in SHR as compared to WKY at all age (30). Moreover, a significant positive correlation between serum HGF concentration and BP was observed in SHR. Elevation of serum HGF concentration can thus be considered a potential index of organ damage induced by hypertension, since there is a significant positive correlation between serum HGF concentration and cardiac hypertrophy. This hypothesis is supported by the above results that both decreased BP and the improvement of such complications as cardiac hypertrophy by AngII blockade decreased the serum
HGF level induced by hypertension. An important question remains: i.e. why was serum HGF elevated in hypertension despite of the decrease in tissue HGF? Although further studies will be needed to clarify this matter, some stimuli such as injurin have been postulated to be increased in serum in response to tissue damage. The circulating level of injurin, which stimulates HGF production (41), might be increased in hypertension. In contrast, circulating Ang II has been shown to be increased in some hypertensive animal models, such as in animals with renovascular hypertension. In these animal models, an increase in circulating Ang II might affect the level of circulating HGF.

Elevation of Serum HGF Concentration in Hypertensive Patients

We have also measured serum HGF concentration in normotensive subjects and hypertensive patients who had never been treated with antihypertensive drugs (4). The serum HGF concentration in untreated hypertensive patients was significantly higher than that in the normotensive group. To further analyze the relationship between serum HGF concentration and BP, we divided the hypertensive group into three stages of hypertension, according to the WHO/ISH 1993 classification. Serum HGF concentration in mild hypertensives (140–180/90–105 mmHg) was significantly higher than that in the normotensive group. Serum HGF concentration in moderate and severe hypertensives (>180/>105 mmHg) was significantly higher than that in normotensive subjects and mild hypertensive patients. Finally, serum HGF concentration in the hypertensive group without complications was significantly positively correlated with systolic and diastolic BP (42).

The effect of complications on serum HGF concentration in hypertensive subjects was further evaluated according to the WHO classification (42). Importantly, serum HGF concentration in hypertensive patients with complications (WHO II/III) was significantly higher than that in patients without complications (WHO I). To exclude the effect of BP, we compared the serum HGF concentrations of hypertensive subjects who showed the same BP level. The serum HGF concentration in hypertensive patients with complications was higher than that in hypertensive patients without complications when comparing case of mild, moderate, or severe hypertension. Interestingly, the serum HGF concentration in hypertensive patients treated with antihypertensive drugs was significantly lower than that in hypertensive patients who had never been treated. There was no significant difference in serum HGF concentration between the normotensive subjects and hypertensive patients without complications who were treated with antihypertensive drugs. Although it remains uncertain whether increased serum HGF affects the pathophysiology of cardiovascular disease, it seems unlikely that an increase in the serum HGF level would prevent or accelerate tissue injury, since the amounts of tissue HGF were much higher than the amounts of circulating HGF in, for example, the heart and blood vessels. For example, the serum HGF level was increased up to 1 ng/ml in most severe hypertensive patients, whereas the vascular and cardiac HGF levels were about 10–100 ng/mg protein. Thus, we postulate that serum HGF level is a potential indicator, rather than a cause, of cardiovascular disease.

Serum HGF Concentration in Diabetic Patients

Given the previous report that high glucose decreased local HGF production in vascular smooth muscle cells and endothelial cells (18, 19), we hypothesized that high glucose affects HGF produc-
tion in various organs, such as the kidney. If so, serum HGF concentration might be decreased in diabetes. In a KKAy mice model of non-insulin-dependent diabetes mellitus, serum HGF concentration was significantly decreased as compared to that in control mice at 14 wk of age (43), while renal and cardiac HGF concentrations were markedly decreased in KKAy mice as compared to those in C57BL mice. Thus, we further evaluated our hypothesis in human subjects in order to study the relationship between serum HGF concentration and the severity of diabetes. As expected, serum HGF concentration was significantly negatively correlated with HbA1c concentration (43). Interestingly, serum HGF concentration in diabetic patients was significantly lower than that in non-diabetic patients. There was no significant difference in serum HGF concentration between male and female subjects in either group.

It is noteworthy that there is a discrepancy between increased serum HGF in hypertension and decreased serum HGF in diabetes, whereas the tissue HGF levels are decreased in both diseases. The liver, lung and kidney are thought to be major sources of serum HGF. High blood pressure in hypertensive patients does not cause injury to the liver or lung, while high blood glucose is known to influence the liver of such patients. Indeed, activation of serum TGF-β, a strong negative regulator of HGF, has been shown to be increased in diabetic patients (44). In hypertension, on the other hand, because the liver and lung are not injured by high blood pressure, they can secrete HGF into serum in response to hypertensive damage. It is likely that this difference in the changes of serum HGF level between hypertension and diabetes is due to the different influences exerted by high blood pressure and high blood glucose on the major source of circulating HGF.

In contrast, the serum HGF concentration in DM patients with hypertension was significantly higher than that in the normal control group or that in DM patients without hypertension. In addition, serum HGF concentration in all DM patients was significantly correlated with systolic, but not with diastolic, BP. Finally, we divided DM patients with hypertension into two groups, a WHO I and a WHO II+III group. The serum HGF concentration in DM patients without hypertensive complications (WHO I patient) was significantly higher than that in the normal control group. The serum HGF concentration in DM patients with hypertensive complications (WHO II+III patients) was higher than that in the other groups. Nishimura et al. examined the relationship between serum HGF concentration and proliferative diabetic retinopathy, which is characterized by the major characteristic of retinal neovascularization (45). Consistent with our findings (43), they found that serum HGF concentration in diabetic subjects without retinopathy was lower than that in non-diabetic subjects. Serum HGF concentration was increased in subjects with proliferative retinopathy who had not undergone photocoagulation, but not in those who had undergone photocoagulation. They concluded that the measurement of serum HGF may be helpful in predicting the presence of proliferative retinopathy in diabetic subjects. Subsequently, they reported that individuals with advanced grades of arteriosclerotic changes had higher serum HGF levels (46). In contrast, they did not find a positive correlation between hypertension and serum HGF concentration. Because they included patients treated with antihypertensive drugs, it would be useful to evaluate the relationship between serum HGF concentration and blood pressure of patients not treated with such drugs. It has also been reported that serum HGF was elevated within 3 h after the onset of chest pain in patients with acute myocardial infarction (47). Interestingly, elevated HGF levels were significantly more frequent than those of creatine kinase within 3 h, and the elevated level correlated well with that of serum creatine kinase at 6-9 h after the onset of acute myocardial infarction. Thus, measurement of HGF is a sensitive method for the early diagnosis of the presence of arteriosclerotic lesions and acute myocardial infarction. Serum HGF concentration may be a useful biochemical parameter for evaluating the development of cardiovascular disease.

HGF belongs to the family of kringle proteins, characterized by a triple disulfide loop structure (kringles) that mediates protein/protein and protein/cell interactions (30). Therefore, HGF may play a role in the regulation of thrombosis and atherosclerosis. The kringle family to which HGF belongs contains tissue-plasminogen activator (t-PA), apolipoprotein (a), plasminogen and urokinase. The influence of other factors related to thrombosis and atherosclerosis on serum HGF concentration was also evaluated, with the result that there was no significant association between serum HGF and total cholesterol concentrations. Similarly, t-PA, PAI-I and Lp (a) concentrations did not show any correlation with serum HGF concentration.

### HGF as a Potential Index of Severity of Vascular Damage in Cardiovascular Disease

As discussed earlier, HGF is a novel member of the family of endothelium-specific growth factors, the serum concentrations of which are significantly...
associated with blood pressure levels and complica-
tion(s) both in hypertensive and diabetic patients.
The local HGF system may be regulated by various
cytokines, including TGF-β and angiotensin II, as
well as by HGF itself in vascular tissues, suggesting
the potential role of HGF as a counter-system
against endothelial dysfunction in cardiovascular
disease (Fig. 5). The measurement of serum HGF
concentration in hypertensive patients might be use-
ful for evaluating the presence of complications and
degree of endothelial dysfunction. In addition,
serum HGF level might be a useful indicator of
such cardiovascular diseases as atherosclerosis and
myocardial infarction, although further studies will
be needed in this regard.

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