Mod Rheumatol (2003) 13:129–134

ORIGINAL ARTICLE

Naoaki Hashimoto · Tsuyoshi Iwasaki · Masayasu Kitano
Atsushi Ogata · Teruaki Hamano

Levels of vascular endothelial growth factor and hepatocyte growth factor in sera of patients with rheumatic diseases

Received: February 19, 2002 / Accepted: August 13, 2002

Abstract Angiogenesis plays an important role in the progression of rheumatic disease. We measured the levels of vascular endothelial growth factor (VEGF) and hepatocyte growth factor (HGF) in sera from patients with rheumatic diseases and investigated whether these angiogenic factors would be useful in the evaluation of rheumatic diseases. Serum VEGF and HGF levels were determined using ELISA in 128 patients with rheumatic diseases and in 11 healthy controls. Serum VEGF and HGF levels were significantly higher in patients with rheumatic diseases compared to healthy controls [VEGF, 312 ± 20 pg/ml versus 61 ± 8 pg/ml (mean ± SE), $P < 0.001$; HGF, 935 ± 36 pg/ml versus 413 ± 49 pg/ml, $P < 0.01$]. Serum VEGF and HGF levels were significantly elevated in patients with adult Still's disease (VEGF, 1021 ± 258 pg/ml; HGF, 1500 ± 295 pg/ml) and were relatively increased in patients with active rheumatoid arthritis (RA) (VEGF, 359 ± 94 pg/ml) and systemic sclerosis (SSc) (VEGF, 356 ± 43 pg/ml; HGF, 1294 ± 224 pg/ml). HGF levels correlated with the clinical course and disease severity in rheumatic disease patients. VEGF levels correlated with the presence of Raynaud's phenomenon ($P < 0.05$), interstitial lung disease (ILD) ($P < 0.05$), and serum KL-6 levels ($P < 0.01$), whereas HGF levels correlated with cryoglobulinemia ($P < 0.05$), ILD ($P < 0.05$), serum C-reactive protein (CRP) ($P < 0.05$), thrombomodulin ($P < 0.05$), and KL-6 levels ($P < 0.05$) in rheumatic disease patients. VEGF levels correlated with the skin scores and KL-6 levels in SSc patients and also correlated with the disease activity of RA patients. These data suggest that serum VEGF and HGF levels are related to rheumatic disease activity and the presence of complications. Analysis of VEGF and HGF may be useful in the clinical evaluation of rheumatic disease patients.

N. Hashimoto · T. Iwasaki (✉) · M. Kitano · A. Ogata · T. Hamano
Division of Rheumatology and Clinical Immunology, Department of Internal Medicine, Hyogo College of Medicine, 1-1 Mukogawa-cho, Nishinomiya 663-8501, Japan
Tel. +81-7-9845-6592; Fax +81-7-9845-6593
e-mail: tsuyo-i@hyo-med.ac.jp

Key words Hepatocyte growth factor (HGF) · KL-6 · Rheumatic diseases (RA) · Vascular endothelial growth factor (VEGF) · Vasculitis

Introduction

Angiogenesis is a critical component of inflammatory disease process. Vascular endothelial growth factor (VEGF) is an angiogenic factor produced by various cells including activated macrophages and keratinocytes and is believed to play an important role in wound healing.[1,2] Hepatocyte growth factor (HGF) is also a potent angiogenic factor[3,4] and contributes to tissue regeneration in various organs.[5]

Recently, it has been reported that serum VEGF levels are significantly increased in systemic sclerosis (SSc) patients and associated with the extent of skin sclerosis and cutaneous ulcerations.[6,7] It has also been noted that serum HGF levels are elevated in response to hypertension and reflect secondary vascular injury.[8] Vascular injury secondary to vasculitis is a critical component of rheumatic diseases. Therefore, we measured the levels of serum VEGF and HGF in patients with rheumatic diseases and investigated the relationship of these angiogenic factors with both clinical and laboratory parameters.

Patients and methods

Patients and serum samples

Serum samples were collected from 128 cases of rheumatic diseases including active rheumatoid arthritis (RA; $n = 22$, 4 males and 18 females; mean age, 54 years; range, 20–71), systemic lupus erythematosus (SLE; $n = 45$, 1 male and 44 females; mean age, 43 years; range, 20–65), and SSc ($n = 32$, 3 males and 29 females; mean age, 52 years; range, 32–69). These patients fulfilled the American College of Rheumatology criteria for RA,[9] SLE,[10] or SSc.[11] Patients with poly-

myositis and dermatomyositis (PM/DM, 5 males and 6 females; mean age, 43 years; range, 24–70), mixed connective tissue disease (MCTD, 11 females; mean age, 41 years; range, 17–65), and adult Still's disease (2 males and 5 females; mean age, 29 years; range, 16–37) satisfied the criteria of Bohan and Peter,[12] Doria et al.[13] and Cush et al.,[14] respectively. Control samples were obtained from healthy blood donors ($n = 11$) and patients with bacterial pneumonia ($n = 10$), osteoarthritis (OA, $n = 10$) and inactive RA ($n = 10$). All patients gave full informed consent before entering the study. Blood samples were stored at −70°C. RA patients received various therapeutic agents including nonsteroid antiinflammatory drugs, disease-modifying antirheumatic drugs, or prednisolone (≦10 mg/day). Active RA was indicated by the presence of tender and swollen joints (>3 joints) and an elevated level of serum C-reactive protein (CRP, >10 mg/l). Conversely, inactive RA was indicated by the absence of tender and swollen joints and low serum CRP levels (<10 mg/l). Patients with SLE, MCTD, PM/DM, and adult Still's disease received various doses of daily prednisolone (5–60 mg/day). However, active clinical disease was present at the time of blood collection and was indicated by symptoms or organ involvement including fever, arthralgia, interstitial lung diseases (ILD), liver dysfunctions, muscle weakness, proteinuria, and renal dysfunction. In some patients with SLE, MCTD, or adult Still's disease, serial samples were taken during the course of clinical disease. Patients with SSc received prednisolone (≦10 mg/day).

VEGF and HGF ELISA

Quantitation of serum VEGF and HGF levels was performed by the enzyme-linked immunosorbent assay (ELISA) employing monoclonal antihuman VEGF and antihuman HGF antibodies (R&D System, Minneapolis, MN, USA). Both standards and samples were assayed in duplicate. The detectable concentration ranges were 31.2–2000 pg/ml and 39–8000 pg/ml for VEGF and HGF ELISA, respectively.

Clinical and laboratory variables.

Labolatory data, obtained from medical records, included hemoglobin (Hb), erythrocyte sedimentation rate (ESR), serum concentrations of CRP, creatinin (CRN), ferritin, cryoglobulin, antiphospholipid antibodies levels, thrombomodulin, and KL-6. The study population was divided into two groups based upon the levels of Hb (≧10 g/dl, <10 g/dl), serum CRN (≦1.7 mg/dl, <1.7 mg/dl), thrombomodulin (≧23.4 U/ml, <23.4 U/ml), KL-6 (≧500 U/ml, <500 U/ml), CRP (≦1.0 mg/dl, <1.0 mg/dl), and ESR (≦20 mm/h, <20 mm/h). ILD was diagnosed on the basis of clinical data and chest radiographs and confirmed in all cases by computed tomography scans. Skin thickness was quantified using the modified Rodnan skin thickness scoring technique[15] in which skin thickness was assessed clinically in 17 body surface areas on a 0–3 scale: 0 = normal, 1 = mild thickness, 2 = moderate thickness, and 3 = severe thickness (maximum score of 51).

Statistical analysis

Group distributions were nonparametrically compared using the Student t test. The association between measurements was evaluated by the product moment correlation or Pearson's correlation coefficient. The varience equality between measurements was confirmed using the F test.

Results

Serum VEGF and HGF levels in patients with rheumatic diseases

Serum VEGF and HGF levels in both patients and controls are shown in Fig. 1. The mean serum VEGF concentration in patients with rheumatic diseases was significantly higher than the level in controls (312 pg/ml versus 61 pg/ml, rheumatic disease group versus controls, $P < 0.001$). In addition, the mean serum HGF concentration in patients with rheumatic disease was significantly higher than the level in controls (935 pg/ml versus 413 pg/ml, rheumatic disease group versus controls, $P < 0.01$) (Fig. 1). In the rheumatic disease group, serum VEGF levels were higher in patients with active RA (359 ± 94 pg/ml) and SSc (356 ± 43 pg/ml), whereas serum HGF levels were higher in SSc patients

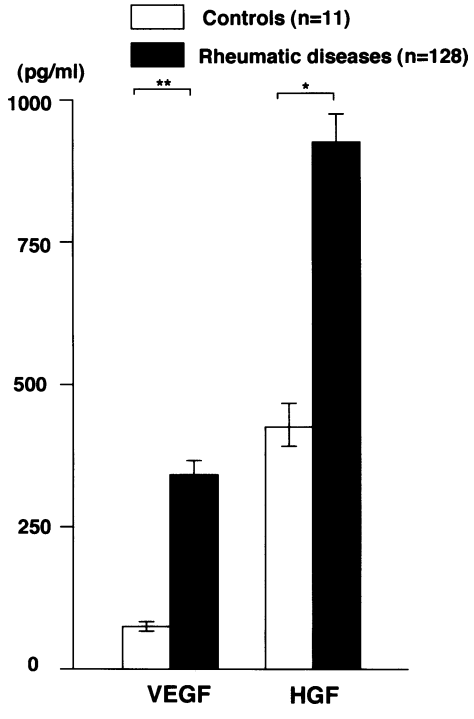

Fig. 1. Serum vascular endothelial growth factor (*VEGF*) and hepatocyte growth factor (*HGF*) levels measured by ELISA for 128 patients with rheumatic diseases and 11 healthy controls. Data represent mean ± SE. * $P < 0.01$, ** $P < 0.001$

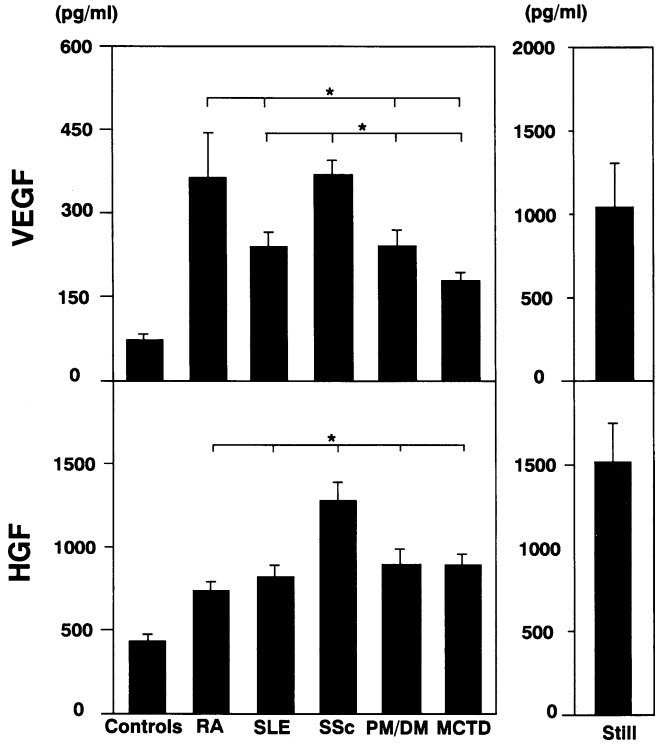

Fig. 2. Serum VEGF and HGF levels in patients with active rheumatoid arthritis (*RA*; $n = 22$), systemic lupus erythematosus (*SLE*; $n = 45$), systemic sclerosus (*SSc*; $n = 32$), polymyositis/dermatomyositis (*PM/DM*; $n = 11$), mixed connective tissue disease (*MCTD*; $n = 11$), and adult Still's disease (*Still*; $n = 7$). Data represent mean ± SE. $^*P < 0.05$

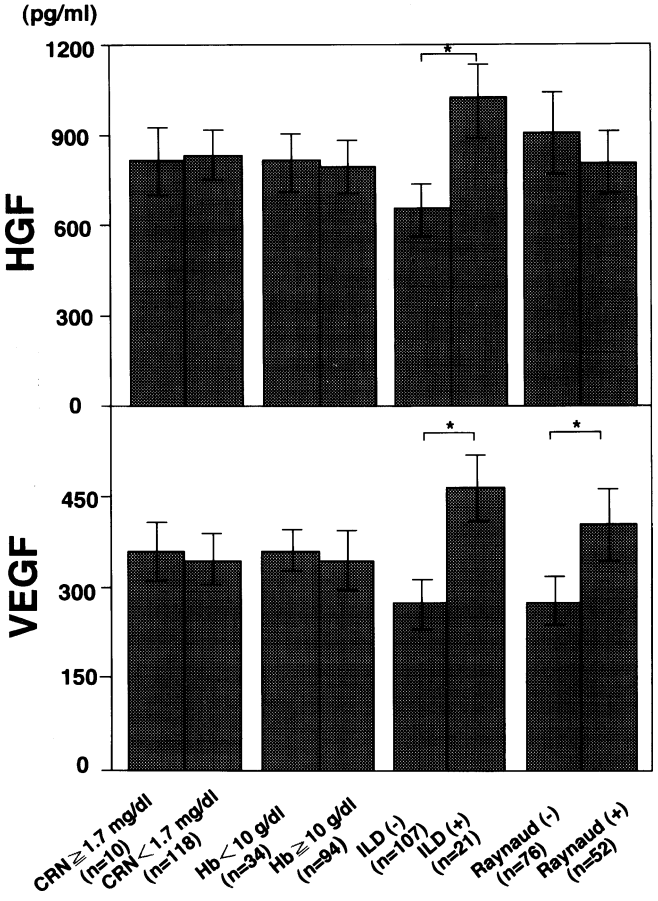

Fig. 3. Correlation between VEGF or HGF levels and the complications of rheumatic diseases. The study population was divided into two groups according to the levels of Hb, serum creatinin (*CRN*), and the presence or absence of interstitial lung disease (*ILD*) or Raynaud's phenomenon (*Raynaud*). Data represent mean ± SE in each group. $^*P < 0.05$

(1298 ± 224 pg/ml). Both serum VEGF and HGF levels were significantly higher in adult Still's disease patients (VEGF, 1021 ± 258 pg/ml; HGF, 1500 ± 295 pg/ml; Fig. 2) compared to patients with other rheumatic diseases.

Correlation with clinical and laboratory findings

We then examined the relationship between serum VEGF or HGF levels and the clinical and laboratory findings of patients. To examine the effect of the complications of rheumatic diseases upon serum VEGF and HGF levels, we divided the study population into two groups based on the levels of Hb, serum CRN, and the presence or absence of Raynaud's phenomenon and ILD. Serum VEGF levels were significantly higher in the patient groups with Raynaud's phenomenon, and ILD serum VEGF levels did not correlate with the level of Hb and serum CRN. Interestingly, levels of serum HGF correlated significantly with the presence of ILD ($p < 0.05$) but not with Raynaud's phenomenon or levels of Hb or serum CRN (Fig. 3). We also divided patients into two groups according to the levels of various markers of (i) vascular injury (cryoglobulin, thrombomodulin, antiphospholipid antibodies), (ii) ILD and KL-6, and (iii) inflammation (CRP and ESR). Serum HGF levels were significantly higher in the groups with elevated levels of cryoglobulins, CRP, thrombomodulin, and KL-6 compared to groups exhibiting low levels of these ($P < 0.05$ in all cases). Serum VEGF levels were higher in the group exhibiting high levels of KL-6 ($p < 0.01$) (Fig. 4). To examine whether serum VEGF or HGF levels are useful markers for the evaluation of the activity of ILD or simply reflect nonspecific pulmonary inflammation, we analyzed serum VEGF and HGF levels in patients with bacterial pneumonia. Serum HGF levels were elevated in patients both with ILD and with bacterial pneumonia (1010 ± 144 pg/ml versus 910 ± 57 pg/ml, $P = 0.47$). However, serum VEGF levels in patients with ILD were significantly higher than in patients with bacterial pneumonia (455 ± 74 pg/ml versus 298 ± 47 pg/ml, $P < 0.05$).

Clinical significance of serum VEGF and HGF levels in SSc and RA patients

Because skin sclerosis and ILD are the main features of SSc, we examined the correlation between serum VEGF or HGF levels and the extent of skin sclerosis or ILD in SSc patients. Serum VEGF levels were significantly higher in patients with skin score ≧20 than patients with skin score

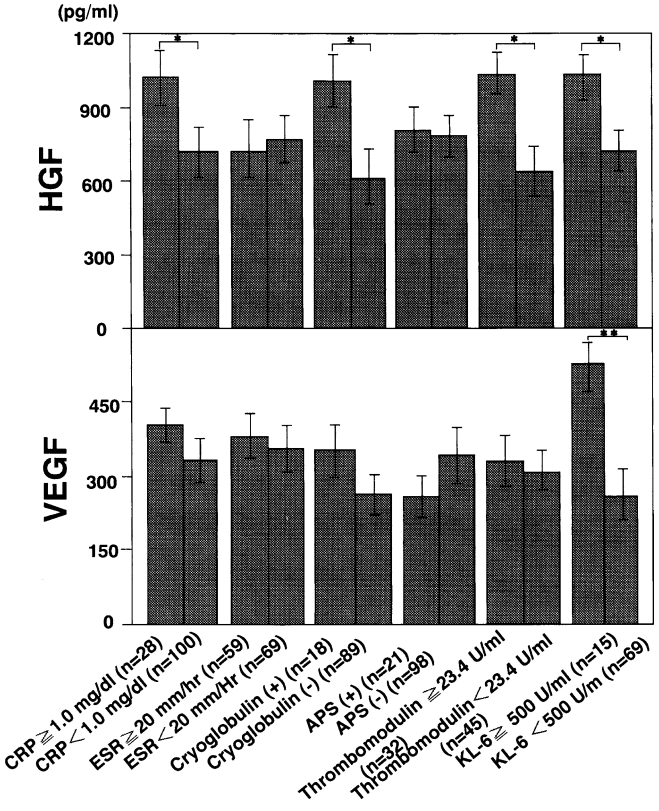

Fig. 4. Correlation between VEGF or HGF levels and the markers of inflammation, vasculitis, and ILD. Data represent mean ± SE in each group. $*P < 0.05$, $**P < 0.01$. *APS*, antiphospholipid syndrome

<20 (438 ± 39 pg/ml versus 269 ± 35 pg/ml, $P < 0.05$) whereas HGF levels were comparable in both groups (1429 ± 158 pg/ml versus 1268 ± 77 pg/ml, $P = 0.49$). Both serum VEGF and HGF levels were significantly higher in the group of patients exhibiting elevated levels of KL-6 (VEGF: 527 ± 67 pg/ml versus 245 ± 45 pg/ml, high KL-6 group versus low KL-6 group, $P < 0.01$; HGF: 2064 ± 114 pg/ml versus 860 ± 57 pg/ml, high KL-6 group versus low KL-6 group, $P < 0.05$, respectively, Fig. 5A). We then examined the correlation between serum VEGF levels and disease activity in patients with RA. Serum VEGF levels were significantly higher in patients with active RA than patients with either inactive RA (359 ± 48 pg/ml versus 118 ± 27 pg/ml, active disease versus inactive disease, $P < 0.05$) or OA (359 ± 48 pg/ml versus 88 ± 17 pg/ml, active RA versus OA, $P < 0.05$). Furthermore, within the active RA group, serum VEGF levels were significantly higher in patients with clinical symptoms of vasculitis such as leg ulcers, rheumatoid nodules, pleuritis, and palpable purpura (855 ± 98 pg/ml versus 182 ± 27 pg/ml, $P < 0.05$; Fig. 5B).

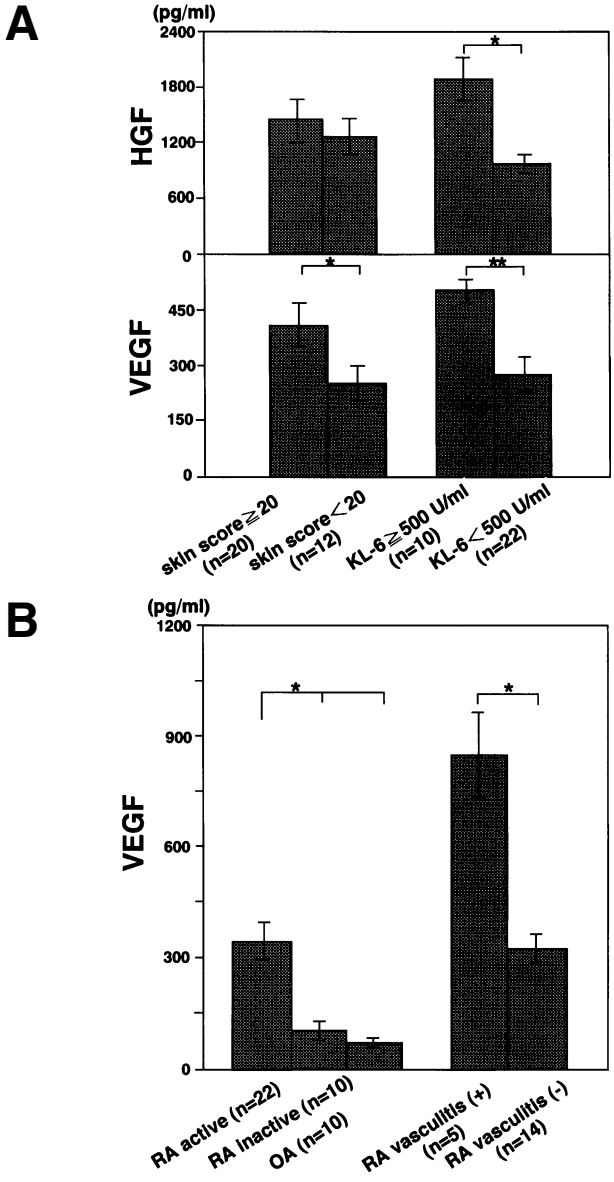

Fig. 5. **A** Correlation between VEGF or HGF levels and skin score or KL-6 levels in SSc patients. **B** Serum VEGF levels in patients with active RA with or without vasculitis, inactive RA, or osteoarthritis (*OA*). Data represent mean ± SE in each group. $*P < 0.05$, $**P < 0.01$

Correlation with disease severity during the clinical course

To further investigate the relevance of VEGF and HGF to the rheumatic disease process, we serially monitored serum VEGF and HGF levels in patients with adult Still's disease, SLE, and MCTD. In patients with adult Still's disease, serum HGF levels became substantially elevated with the development of pyrexia and arthralgia but fell following successful treatment with corticosteroids. Furthermore, serum HGF levels were closely correlated with serum ferritin concentration throughout the observed disease course. In contrast to serum HGF levels, serum VEGF levels did not correlate with clinical symptoms or serum ferritin levels (Fig. 6A). Moreover, serum HGF levels also correlated with disease activity in patients with SLE or MCTD. Two patients with active SLE and one MCTD patient with active clinical symptoms including pyrexia and arthralgia were treated with prednisolone. The serum HGF levels fell in accordance with the reduction in SLE activity (SLEDAI score fell from 12 to 2 and 11 to 1 with treatment) or the

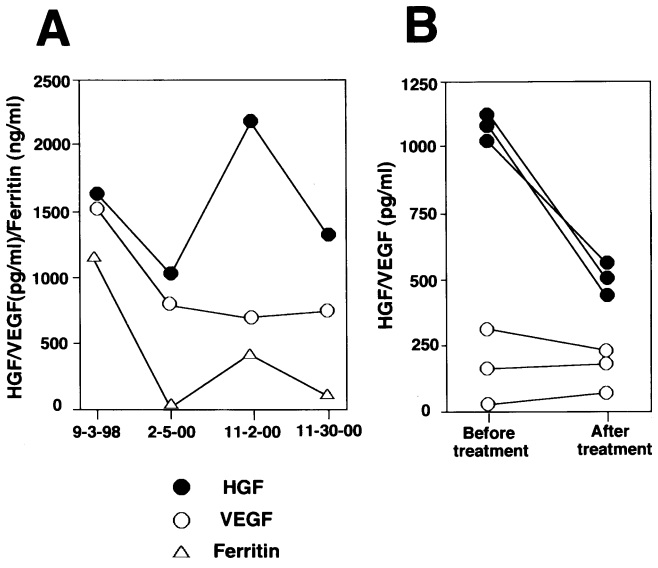

Fig. 6. Correlation between VEGF or HGF levels and disease activity. **A** Serum VEGF (○), HGF (●), and ferritin levels (△) in serial samples taken during the clinical course of a patient with adult Still's disease. **B** Serum VEGF (○) and HGF (●) in serum from three patients with rheumatic diseases (two patients with SLE and one patient with MCTD)

resolution of active clinical symptoms of MCTD including pyrexia and arthralgia (Fig. 6B).

Discussion

The first major finding of this study is that patients with rheumatic disease exhibit significantly elevated serum VEGF and HGF levels compared to control subjects. Serum VEGF levels were higher in patients with RA or SSc than in patients with SLE, PM/DM, or MCTD. Interestingly, serum VEGF levels reflected disease activity and the presence of vasculitis in RA patients. Similarly, serum VEGF levels reflected the presence of vasculitis in SLE patients because patients exhibiting cutaneous or vascular manifestations such as ulceration, livedo reticularis, and urticaria had significantly higher serum VEGF levels. Previous work has suggested that VEGF may play a role in the pathogenesis of RA. For example, synovial fluid derived from RA patients exhibits significantly higher levels of VEGF compared to synovial fluid from patients with other forms of arthritis including OA.[16,17] In addition, VEGF is highly expressed in the inflamed synovium where it may be expressed by both synovial fibroblasts and activated macrophages.[17,18] Important stimuli for VEGF release include various inflammatory mediators such as IL-1, IL-6, and transforming growth factor-beta (TGF-β), which are involved in the pathogenesis of RA.[19–21] Furthermore, it has been demonstrated that the interaction between CD40 on the cell surface of synovial fibroblasts and CD40L expressed by activated T cells may be directly involved in the neovascularization of the rheumatoid synovitis by enhancing VEGF production.[22] In support of our findings, Kikuchi et al. reported significant elevation of serum VEGF levels in RA patients,[6] suggesting that the increased serum VEGF levels of RA patients may reflect inflammatory processes and neovascularization occurring with the inflamed rheumatoid synovium.

Hypoxia upregulates both VEGF protein and mRNA expression in fibroblasts.[23–25] Previous reports indicated that serum VEGF levels are significantly increased in SSc patients and are associated with the extent of skin sclerosis and cutaneous ulcerations,[6,7] thereby suggesting that VEGF may be induced as a consequence of the hypoxia resulting from vascular injury in SSc patients. Consistent with previous findings, we found that serum VEGF levels were significantly increased in SSc patients and correlated with the extent of skin sclerosis. We also demonstrated that serum VEGF levels correlated with Raynaud's phenomenon, indicating that serum VEGF levels may be predictive of the development of vasculitis in SSc patients. HGF levels were also significantly increased in SSc patients and correlated with a marker of endothelial injury (thrombomodulin). HGF is an endothelium-specific mitogen and is the most potent growth factor for human aortic endothelial cells.[26] Nakamura et al. have reported that serum HGF levels are significantly elevated in patients with hypertension and are dependent upon the severity of hypertension, suggesting that HGF may be a novel marker of hypertension severity. They speculated that elevation in serum HGF acts to counteract hypertension-mediated vascular endothelial cell injury.[8] Because patients with SSc exhibit a variety of organ damage secondary to the vasculitis, elevated serum HGF levels may well reflect endothelial cell injury induced by vasculitis.

Serum VEGF and HGF levels were both extremely elevated in the sera of patients with adult Still's disease. Marked elevation of circulating serum levels of inflammatory cytokines is well documented in these patients with cytokine levels correlating with disease severity.[27,28] The present study demonstrated that serum levels of angiogenic cytokines are extremely high in patients with adult Still's disease, suggesting potential involvement in the pathogenesis of this disease. In addition, unlike VEGF, serum HGF levels correlated with parameters of the clinical severity of adult Still's disease and fell following treatment with corticosteroids. Similarly, serum HGF levels correlated with SLE and MCTD disease activity and with various inflammation and vasculitis markers, including CRP, thrombomodulin, and cryoglobulins. Although it is currently unclear why HGF levels but not VEGF levels correlate with disease activity, these observations suggest that HGF may be a useful marker of rheumatic disease activity.

Both serum VEGF and HGF levels significantly correlated with ILD and its marker (KL-6). Alveolar type II epithelial cell proliferation is believed to be critical for the restoration of gas exchange units following diffuse alveolar damage. KL-6 is a mucin-like glycoprotein that is strongly expressed on alveolar type II epithelial cells[29] and is a useful serum marker of ILD severity.[30,31] Elevated serum HGF levels have been documented in patients with lung disease,[32]

and HGF is mitogenic for alveolar type II epithelial cells in vitro and in vivo.[33,34] VEGF is abundant in the lung, and serum VEGF levels were also elevated in ILD patients.[6,35] Taken together, we suggest that both VEGF and HGF may act as a pulmonary trophic factors during tissue regeneration and remodeling following lung injury.

In conclusion, production of the angiogenic factors VEGF and HGF was increased in patients with rheumatic diseases with serum levels correlating with disease severity and the presence of complications. Thus, analysis of serum VEGF and HGF levels may be useful in the evaluation of the rheumatic disease status of patients.

Acknowledgment We are grateful to Ms. Aki Nomura for assistance with the ELISA of VEGF and HGF.

References

1. Berse B, Brown LF, Van De Water L, Dvorak HF, Senger DR. Vascular permeability factor (vascular endothelial growth factor) gene is expressed differentially in normal tissues, macrophages, and tumors. Mol Biol Cell 1992;3:211–20.
2. Brown LF, Yeo KT, Berse B, Yeo TK, Senger DR, Dvorak HF, et al. Expression of vascular permeability factor (vascular endothelial growth factor) by epidermal keratinocytes during wound healing. J Exp Med 1992;176:1375–9.
3. Grant DS, Kleinman HK, Goldberg ID, Bhargaba MM, Nickloff BJ, Kinsella JL, et al. Scatter factor induces blood vessel formation in vivo. Proc Natl Acad Sci USA 1993;90:1937–41.
4. Bussolino F, Di Renzo MF, Ziche M, Bocchietto E, Olivero M, Naldini L, et al. Hepatocyte growth factor is a potent angiogenic factor which stimulates endothelial cell motility and growth. J Cell Biol 1992;119:629–41.
5. Zarnegar R, Michalopoulos GK. The many faces of hepatocyte growth factor: from hepatopoiesis to hematopoiesis. J Cell Biol 1995;129:1177–80.
6. Kikuchi K, Kubo M, Kadono T, Yazawa N, Ihn H, Tamaki K. Serum concentrations of vascular endothelial growth factor in collagen diseases. Br J Dermatol 1998;139:1049–51.
7. Yoon CH, Min DJ, Cho ML, Park KS, Seo Y, Choi JJ, et al. Elevated vascular endothelial growth factor in patients with systemic sclerosis. Arhtritis Rheum 1999;42:A1179.
8. Nakamura S, Moriguchi A, Morishita R, Aoki M, Yo Y, Hayashi S, et al. A novel vascular modulator, hepatocyte growth factor (HGF), as a potent index of the severity of hypertension. Biochem Biophys Res Commun 1998;242:238–43.
9. Arnett FC, Edworthy SM, Bloch DA, McShane DJ, Fries JF, Cooper NS, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988;31:315–24.
10. Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982;25:1271–7.
11. Subcommittee for Scleroderma Criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Arthritis Rheum 1980;23:581–90.
12. Bohan A, Peter JB. Polymyositis and dermatomyositis. N Engl J Med 1975;292:344–7.
13. Doria A, Ghirardello A, de Zambiasi P, Ruffanti A, Gambari PF. Japanese diagnostic criteria for mixed connective tissue disease in Caucasian patients. J Rheumatol 1992;19:259–64.
14. Cush JJ, Medsger TA Jr, Christy WC, Hebert DC, Cooperstein LA. Adult-onset Still's disease: clinical course and outcome. Arthritis Rheum 1987;30:186–94.
15. Clements P, Lachenbruch P, Seibold JR, White B, Weiner S, Martin RW, et al. Inter- and intraobserver variability of total skin thickness score (modified Rodnan TTS) in systemic sclerosis. J Rheumatol 1995;22:1281–5.
16. Koch AE, Harlow LA, Haines GK, Amento EP, Unemori EN, Wong WL, et al. Vascular endothelial growth factor: a cytokine modulating endothelial function in rheumatoid arthritis. J Immunol 1994;152:4149–56.
17. Fava RA, Olsen NJ, Spencer-Green G, Yeo KT, Yeo TK, Berse B, et al. Vascular permeability factor/endothelial growth factor (VPF/VEGF): accumulation and expression in human synovial fluids and rheumatoid synovial tissue. J Exp Med 1994;180:341–6.
18. Nagashima M, Yoshino S, Ishiwata T, Asano G. Role of vascular endothelial growth factor in angiogenesis of rheumatoid arthritis. J Rheumatol 1995;22:1624–30.
19. Ben-Av P, Crofford LJ, Wilder RL, Hla T. Induction of vascular endothelia growth factor expression in synovial fibroblasts by prostaglandin E and interleukin-1: a potential mechanism for inflammatory angiogenesis. FEBS Lett 1995;372:83–7.
20. Cohen T, Nahari D, Cerem LW, Neufeld G, Levi BZ. Interleukin 6 induces the expression of vascular endothelial growth factor. J Biol Chem 1996;271:736–41.
21. Petrovaara L, Kaipainen A, Mustonen T, Orpana A, Ferrara N, Saksela O, et al. Vascular endothelial growth factor is induced in response to transforming growth factor-beta in fibroblastic and epithelial cells. J Biol Chem 1994;269:6271–4.
22. Cho CS, Cho ML, Min SY, Kim WU, Min DJ, Lee SS, et al. CD40 engagement of synovial fibroblast up-regulates vascular endothelial growth factor. J Immunol 2000;164:5055–61.
23. Jackson JR, Minton JA, Ho ML, Wei N, Winkler JD. Expression of vascular endothelial growth factor in synovial fibroblasts is induced by hypoxia and interleukin 1-beta. J Rheumatol 1997;24:1253–9.
24. Berse B, Hunt JA, Diegel RJ, Morganelli P, Yeo K, Brown F, et al. Hypoxia augments cytokine (transforming growth factor-beta (TGF-beta) and IL-1)-induced vascular endothelial growth factor secretion by human synovial fibroblasts. Clin Exp Immunol 1999;115:176–82.
25. Ikeda E, Achen MG, Breier G, Risau W. Hypoxia-induced transcriptional activation and increased mRNA stability of vascular endothelial growth factor in C6 glioma cells. J Biol Chem 1995;270:19761–6.
26. Nakamura Y, Morishita R, Higaki J, Kida I, Aoki M, Moriguchi A, et al. Hepatocyte growth factor is a novel member of endothelium-specific growth factors: additive stimulatory effect of hepatocyte growth factor with basic fibroblast growth factor, but not vascular endothelial growth factor. J Hypertens 1996;14:1067–72.
27. Hoshino T, Ohta A, Yang D, Kawamoto M, Kikuchi M, Inoue Y, et al. Elevated serum interleukin 6, interferon-γ, and tumor necrosis factor-α levels in patients with adult Still's disease. J Rheumatol 1998;25:396–8.
28. Kawashima M, Yamamura M, Taniai M, Yamauchi H, Tanimoto T, Kurimoto M, et al. Levels of interleukin-18 and its binding inhibitors in the blood circulation of patients with adult-onset Still's disease. Arthritis Rheum 2001;44:550–60.
29. Kohono N, Akiyama M, Kyoizumi S, Hakoda M, Kobuke K, Yamakido M. Detection of soluble tumor-associated antigens in sera and effusions using novel monoclonal antibodies, KL-3 and KL-6, against lung adenocarcinoma. Jpn J Clin Oncol 1988;18:203–16.
30. Sato S, Nagaoka T, Hasegawa M, Nishijima C, Takehara K. Elevated serum KL-6 levels in patients with systemic sclerosis: association with the severity of pulmonary fibrosis. Dermatology 2000;200:196–201.
31. Fukuya S, Oshima H, Kato K, Komatsu Y, Matsumura H, Ishii K, et al. KL-6 as a novel marker for activation of interstitial pneumonia in connective tissue diseases. Rheumatol Int 2000;19:223–5.
32. Maeda J, Ueki N, Hada T, Higashino K. Elevated serum hepatocyte growth factor/scatter factor levels in inflammatory lung disease. Am J Respir Crit Care Med 1995;152:1587–91.
33. Ohmichi H, Matsumoto K, Nakamura T. In vivo mitogenic action of HGF on lung epithelial cells: pulmotropic role in lung regeneration. Am J Physiol 1996;270:L1031–9.
34. Mason RJ, Leslie CC, McCormick-Shannon K, Deterding RR, Nakamura T, Rubin JS, et al. Hepatocyte growth factor is a growth factor for rat alveolar type II cells. Am J Respir Cell Mol Biol 1994;11:561–7.
35. Monacci WT, Merrill MJ, Oldfield EH. Expression of vascular permeability factor/vascular endothelial growth factor in normal rat tissues. Am J Physiol 1993;264:C995–1002.