Expression of Hepatocyte Growth Factor/c-met by RT-PCR in Meningiomas

Na Rae Kim · Yang Seok Chae[1]
Weon Jeong Lim[2] · Seong Jin Cho[3]

Department of Pathology, Gachon University Gil Hospital, Incheon; [1]Department of Pathology, Korea University Anam Hospital, Korea University College of Medicine; [2]Department of Neurochiatry, Ewha Womans University Mokdong Hospital, Ewha Womans University School of Medicine; [3]Department of Pathology, Kangdong Sacred Heart Hospital, Hallym University College of Medicine, Seoul, Korea

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Corresponding Author
Seong Jin Cho, M.D.
Department of Pathology, Sacred Heart Hospital, Hallym University College of Medicine, 445 Gil-dong, Gangdong-gu, Seoul 134-701, Korea
Tel: +82-2-2224-2557
Fax: +82-2-2224 2114
E-mail: embrael21@empal.com

Background: Hepatocyte growth factor (HGF) is a potent mitogenic cytokine. C-met protein, which is known to be the HGF receptor has transmembrane tyrosine kinase activity and is encoded by the c-met oncogene. The HGF/c-met signaling pathway may play various roles in the carcinogenesis of various organs. **Methods:** We examined HGF and c-met mRNA expression by utilizing reverse transcription polymerase chain reaction on 40 surgically resected intracranial meningiomas (25 benign, 10 atypical, and 5 anaplastic cases). **Results:** An HGF overexpression was detected in 28%, 50%, and 80% of the benign, atypical and anaplastic meningiomas, respectively; a high expression of HGF or the coexpression of HGF/c-met was detected in the high grade meningiomas (the atypical and anaplastic cases, p = 0.046, p = 0.014). An HGF expression was statistically significant in the recurrent meningiomas (p = 0.003), and HGF expression was significantly lower than c-met mRNA expression in benign meningiomas (p = 0.034). **Conclusions:** There was no correlation between histologic subtypes and HGF/c-met expression. Determination of HGF expression can be used as a molecular predictor for recurrence of meningioimas. These results suggest that HGF and c-met expression in meningiomas may be associated with anaplastic progression.

Key Words: Hepatocyte growth factor; c-met; Meningioma; Neoplasm recurrence, local; Reverse transcription polymerase chain reaction

Meningiomas are classified as benign, atypical or anaplastic. Most of them belong histologically to the World Health Organization (WHO) grade I. However, their clinical outcomes vary for recurrence; 25% of meningiomas show local recurrences.[1] A few factors can be used as predictors for relapse: the vascular endothelial growth factor (VEGF) concentration, cellular atypia and markers of cell proliferation.[2-4] Neither the histopathologic nor the clinical data of meningiomas are currently accepted as reliable recurrence predictors because of their low accuracy. Molecular studies on the recurrence of meningioma have been described in the literature.[5] The expression of hepatocyte growth factor (HGF) (scatter factor [SF]) or c-met in meningiomas has recently received attention.[6,7] HGF was originally identified as a growth factor for hepatocytes, and HGF dissociates epithelial cells and increases their motility.[8,9] c-met tyrosine kinase participates in cancer invasion, angiogenesis and metastasis in a wide variety of neoplastic cells; the expression of HGF/c-met has been detected in breast carcinomas, lung carcinomas and prostatic carcinomas, as well as hepatocellular carcinomas.[10-13] However, little is known about its expression and function in prima-ry tumors of the central nervous system. Here, we investigated the expression of HGF and c-met in meningiomas that were with or without recurrence by performing reverse transcription polymerase chain reaction (RT-PCR).

MATERIALS AND METHODS

Materials

The meningioma specimens were selected from the pathology files of the Hallym University Kangdong Sacred Heart Hospital between 1995 and 2001. Only cases with sufficient data for analysis and a minimum of 5 year of follow-up were included in the study. All the specimens had both tumor and adjacent normal brain tissue. The patients' medical charts and radiographic files were retrospectively reviewed for the clinical, radiographic, operative and pathological data. Patients who had previously been operated on or had received chemotherapy or radiotherapy were not included in the study.

Pathologic examination

All the specimens were fixed in 10% formalin and then embedded in paraffin. The formalin-fixed and paraffin-embedded tumor samples from forty cases were stained with hematoxylin and eosin. All the meningiomas were reclassified under light microscopy according to the 2007 WHO grading system.[1]

RT-PCR for the extraction of HGF and c-met mRNA

Tissue samples

The fresh tumor tissue was collected at the same time as the paraffin blocks of the tumors were made. As controls, we used the fresh brain and leptomeningeal tissue taken from autopsy specimens of 5 cases.

RT-PCR

The total RNA was extracted from the tissue samples by Trizol (GIBCO, Gaithersburg, MD, USA). For cDNA synthesis, 1 μg of total RNA was reverse-transcribed using a random primer and Superscript reverse-transcriptase (GIBCO, Grand Island, NY, USA). The DNA sequences of primers used were as follows: *HGF* (sense, 5´-TCACGAGCATGACATGACTCC-3´; anti-sense, 5´-AGCTTACTTGCATCTGGTTCC-3´), *c-met* (sense, 5´-ACAGTGGCATGTCAACATCGCT-3´; antisense, 5´-GCTCGGTAGTCTACAGATTC-3´), and *β-actin* (sense, 5´-AGGCCAACCGCGAGAAGATGACC-3´; anti-sense, 5´-GAAGTCCAGGGCGACGTAGCAC-3´). For PCR, the cDNA samples were brought to a final concentration of 50 mM KCl, 10 mM Tris (pH 8.3), 1.5 mM MgCl$_2$, 0.001% gelatin, 200 μM dNTPs and 7 mM anti-Taq polymerase monoclonal antibody (Clontech, Mountain View, CA, USA). In addition, each sample contained 0.1 pmol of both the reverse and forward primers and 2.5 U of Taq polymerase (Takara, Tokyo, Japan). PCR was carried out in a programmable heating block (Perkin Elmer Cetus, Norwalk, CT, USA) using five cycles that consisted of denaturation at 94℃ for 1 minute, annealing at 58℃ for 1 minute and extension at 72℃ for 1 minute 15 seconds, and this was followed by 30 cycles consisting of 94℃ for 10 seconds, 58℃ for 30 seconds and 72℃ for 1 minute. PCR products were then loaded onto a 1.5% agarose gel with ethidium bromide for electrophoresis. cDNA bands were photographed using a UV illuminator and analyzed with a Thermal Imaging System FTI-500 (Pharmacia, Uppsala, Sweden). Semi-quantitative analyses of c-met and HGF mRNA expression was made. The relative band intensity of both genes was quantified as ratios to β-actin, estimated by densitometry of the ethidium bromide-stained RT-PCR products.

Statistical analysis

SPSS ver. 10.0 (SPSS Inc., Chicago, IL, USA) was used for data analysis. The association between categorical variables was assessed by Chi-squared tests. Statistical significance was set at $p < 0.05$.

RESULTS

The clinicopathological results

Thirteen males and twenty-seven female patients were included in this study. Their ages ranged from 27 to 67 years. Of the 40 cases, 25 were categorized as benign meningiomas (grade I, 62.5%), 10 were categorized as atypical meningiomas (grade II, 25%) and 5 were categorized as anaplastic meningiomas (grade III, 12.5%). Except for the anaplastic meningiomas, all thirty-five cases of the benign and atypical meningiomas underwent gross total resection. They were classified as the meningotheliomatous type (n = 23), the transitional type (n = 7), the fibrous type (n = 3), and the psammomatous type (n = 2). Two cases of benign meningiomas and three cases of atypical meningiomas with completely resected meningiomas recurred within 5 to 12 years of follow-up. The interval between resection and recurrence ranged from 41 to 93 months (mean, 58.6 months).

The expression of HGF and c-met mRNA by RT-PCR

The expression of HGF mRNA and c-met mRNA was detected in both the normal meningothelial cells and in tumor tissue, although they were minimally expressed in the normal meningothelial cells. When the expression was set at one in the normal lymph nodes, the average value for the expression of HGF and c-met in the normal meningothelial cells and meningioma tissue was 0.79 (standard deviation [SD], 0.25) and 0.84 (SD, 0.33), respectively. To assess the overexpression of mRNA in meningioma, the sum of double the SD and the mean value of the normal brain and the meningeal tissue were regarded as a baseline value. The baseline HGF value of the positive cases was 1.29 and that of c-met was 1.5 (Fig. 1).
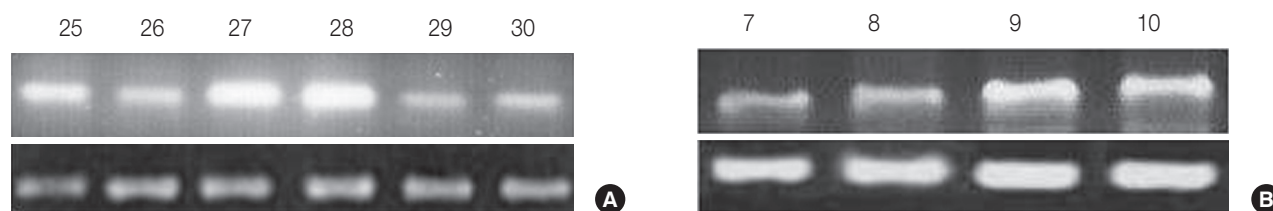
25 26 27 28 29 30

7 8 9 10

Fig. 1. (A) Reverse transcription polymerase chain reaction (RT-PCR) analysis for hepatocyte growth factor in the meningiomas. Cases 27 and 28 show overexpression of mRNA. (B) RT-PCR analysis for c-met in the meningiomas. Cases 9 and 10 show overexpression of c-met mRNA.

The expression of HGF and c-met according to the histologic grade

The mRNA of HGF was expressed in 28% of the benign meningiomas (7/25), 50% of the atypical meningiomas (5/10) and 80% of the anaplastic meningiomas (4/5). The mRNA of c-met was expressed in 48% of the benign meningiomas (12/25), 60% of the atypical meningiomas (6/10) and 100% of the anaplastic meningiomas (5/5). The expression of c-met and/or HGF showed no statistically significant differences between each grade when compared with three grades of meningiomas. The expression of c-met mRNA was statistically significantly higher than that of the HGF mRNA expression in the grade I meningiomas (p = 0.034).

The expression of HGF and c-met according to the histologic type

Among the 35 cases of meningiomas of grades I and II, HGF mRNA was frequently expressed in the transitional (71.4%, 5/7), fibrous (33.3%, 1/3) and meningotheliomatous types (26.1%, 6/23). However no statistically significant correlation was found between the histologic type and the expression of HGF or c-met mRNA (p = 0.080, p = 0.320, respectively).

The expression of HGF and c-met according to recurrence

Among the 35 cases of benign and atypical meningiomas, the HGF expression was significantly higher in the recurrent meningiomas than that in those meningiomas without recurrence (p = 0.003). No statistically significant differences were found between the coexpression of HGF/c-met or the expression of c-met and recurrence (p = 0.408, p = 0.397). These results are shown in Table 1 and Fig. 1.

Semi-quantitative RT-PCR analysis of HGF and c-met expression

1.5% agarose gel band density signals corresponding to both gene expressions were normalized relative to β-actin for each

Table 1. RT-PCT for the HGF and the c-met expression in meningioma according to the clinicopathological factors

Clinicopathologic parameters	HGF(+)	c-met(+)	Coexpression of HGF(+)/c-met(+)
WHO grade of meningiomas			
WHO grade I (n = 25)	7 (28)	12 (48)	3 (12)
WHO grade II + III (n = 15)	9 (60)	11 (73.3)	7 (46.7)
p-value	0.046	0.117	0.014
Histological types of the grade I and II meningiomas			
Transitional (n = 7)	5 (71.4)	4 (57.1)	3 (42.9)
Fibrous (n = 3)	1 (33.3)	1 (33.3)	1 (33.3)
Meningotheliomatous (n = 23)	6 (26.1)	10 (43.5)	2 (8.7)
Psammomatous (n = 2)	0 (0)	2 (100)	0 (0)
p-value	0.080	0.320	0.088
Recurrence of the grade I and II meningiomas			
Recurrence (n = 5)	5 (100)	2 (40)	2 (40)
No recurrence (n = 30)	7 (23.3)	16 (53.3)	0 (0)
p-value	0.003	0.397	0.408

Values are presented as number (%).
RT-PCR, reverse transcription polymerase chain reaction; HGF, hepatocyte growth factor; WHO, World Health Organization.

sample and quantified. Significantly higher expression of HGF was noted according to the grade (p < 0.01). Also, anaplastic meningiomas showed higher expression of both genes compared to benign and atypical meningiomas. There is no significant difference in c-met expression among benign, atypical and anaplastic meningiomas. These semi-quantitative results were consistent with above results and are shown in Fig. 2.

DISCUSSION

In this report, we have compared the expression of HGF and c-met in meningiomas as measured by RT-PCR. HGF is a well known factor that promotes tumor cell invasiveness and is a protein that consists of a heavy chain (60 kD) with four domains and a light chain (32 kD). It binds through its tyrosine-kinase receptor, which is a product of the proto-oncogene c-met. HGF is a powerful angiogenic factor for endothelial cells both *in vitro* and *in vivo*.[14] The HGF and c-met signaling pathway is of cen-
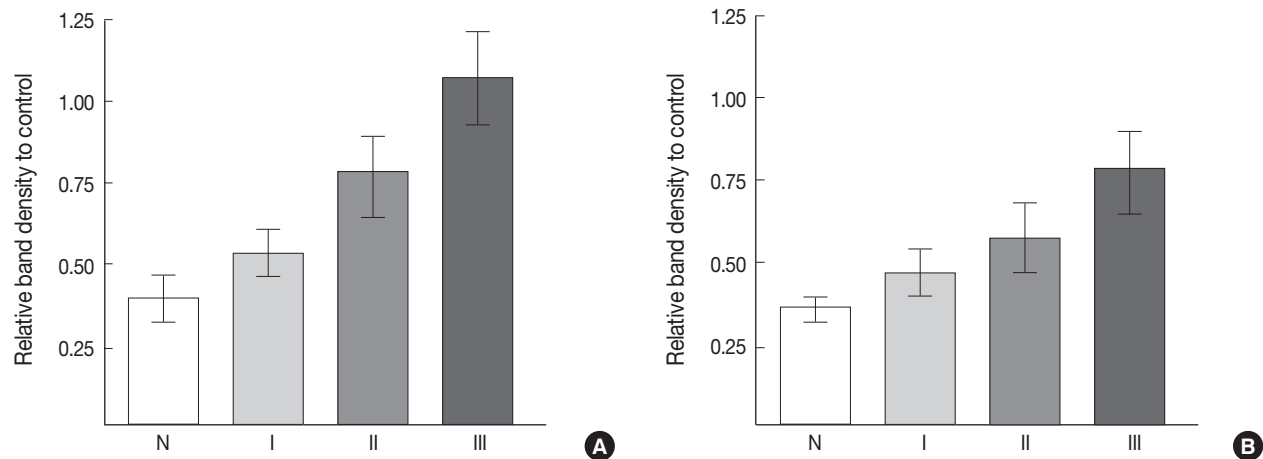
Fig. 2. Semi-quantitative reverse transcription polymerase chain reaction analyses of hepatocyte growth factor mRNA (A) and c-met mRNA (B) expression are shown according to normal control (N) and meningiomas of grade I (I), grade II (II) and grade III (III). Note the bars showing the relative band density of mean and standard deviation of each group.

tral importance during development as well as in tumorigenesis,[8,11] and this pathway is activated in an autocrine fashion in a variety of tumors such as breast, ovary, lung, liver, kidney, brain, and others.[12,13,15-17] HGF/c-met has also been found in the brain in astrocytes, gliomas and meningiomas.[18,19] Previous studies have shown that HGF increases the permeability of the blood-brain barrier independently of the VEGF expression, and this possibly occurs by the induction of endothelial fenestrations and by the tumoral expression of proteases such as urokinase and extracellular matrix metaloproteins.[20] HGF/c-met are simultaneously expressed in human cultured glioma cells with an autocrinous effect that induces cell proliferation and migration. In addition, HGF/c-met are expressed in brain tumors with the expression frequently correlating with the tumor grade and a poor prognosis.[16,18] Several studies have focused on HGF and c-met in meningiomas.[16,18,21-23] In Moriyama *et al.*'s study,[16] HGF that was evaluated by RT-PCR was preferably expressed in the transitional (50% [2/4]) and fibrous meningiomas (100% [2/2]) as compared with that of the meningotheliomatous type (13% [1/8]). These authors suggest that autocrine production of HGF is involved in the establishment of a more fibrous morphology of the meningioma cells. The expression of c-met and HGF and their coexpression were found in 86% (12/14), 36% (5/14) and 29% (4/14) of meningiomas, respectively. In the present study, c-met mRNA, HGF mRNA and their coexpression were expressed in 58% (23/40), 40% (16/40) and 25% (10/40) of the meningiomas, respectively. Moriyama *et al.*'s findings[16] are different from those of the present study in which the morphologic type has no statistical relationship with the HGF/c-met expression. Moriyama *et al.*'s study[16] and the present series share a

higher incidence of a c-met expression in meningiomas, suggesting that c-met may have biological role in the low grade meningiomas. Any association of the expression of HGF or c-met with recurrence was not assessed in Moriyama *et al.*'s study.[16] As a molecular predictor of recurrence of meningiomas, Arrieta *et al.*[18] described that a high level of HGF in the meningiomas was associated with long term recurrence, as well as with the mitotic index and the proliferation index of meningiomas, as was previously observed.[2-4] For the meningiomas showing a high intratumoral HGF concentration (more than 4,000 pg/mL [5/11]) in the present study, the percentage of recurrences, the mitotic index and the cell proliferation index were higher (p< 0.01) compared with those values for the meningiomas with a lower HGF concentration, as measured by RT-PCR. The present study showed that the coexpression of HGF and c-met has no association with recurrence, but it has an association with the histologic grade of meningiomas, whereas Martínez-Rumayor *et al.*'s study[21] revealed the coexpression of HGF and c-met had a significant association with the proliferative indices and recurrence. The present study and Martínez-Rumayor *et al.*'s study[21] are discordant with the study of Karja *et al.*[23] No significant differences were found in their study when HGF or c-met was independently compared in the meningiomas with or without recurrence. They suggest that the coexpression of HGF and c-met mRNAs in the meningiomas could be used as a predictor of recurrence even for the totally resected meningiomas. Yet in Lamszus *et al.*'s study,[22] HGF/SF was not associated with a higher malignancy grade and was not related to invasive meningiomas even though HGF is a well known factor that promotes tumor cell invasiveness. HGF was not associated with

Table 2. Previous studies on HGF and c-met in meningiomas

References	Materials	Methods		Summary of results
Moriyama *et al.*[16]	Meningioma (WHO grade I), glioma (grade III, IV), schwannoma	HGF, c-met	RT-PCR, immunohistochemistry (c-met)	Consistent c-met mRNA expression in meningioma (8/8) and schwannoma (12/14), supporting their biological role in meningioma and schwannoma All the studied meningiomas (4/4) by c-met immunostaining, which was concordant with the results of RT-PCR Transional and fibrous meningiomas are related to HGF/c-met. No mention about recurrent meningioma
Arrieta *et al.*[18]	Meningioma, glioma, pituitary adenoma, oligodendroglioma, chordoma	HGF	ELISA	A high HGF concentration (15,844 pg/mL) in malignant glioma and in meningioma A high HGF concentration (22,887 pg/mL) in recurrent meningioma
Lamszus *et al.*[22]	Meningioma (WHO grade I, II, III)	HGF	ELISA	HGF is not associated with the grade of meningioma, the microvessel density or invasiveness.
Martínez-Rumayor *et al.*[21]	Meningioma (WHO grade I, II)	HGF, c-met	Immunohistochemistry	The coexpression of HGF and c-met in meningiomas showed an association with the cell proliferation index and with recurrence, supporting that determination of HGF and c-met may be used as a molecular predictor of recurrence. A high HGF expression in the low grade meningiomas with no statistical significance
Karja *et al.*[23]	Meningioma (WHO grade I)	HGF, Ki-67	Immunohistochemistry	The expression of none of the proteins or correlation between protein expressions previously reported to be of significance regarding recurrence of grade I meningiomas
Kim *et al.* (this study)	Meningioma (WHO grade I, II, III)	HGF, c-met	RT-PCR	A high HGF expression in recurrent meningiomas, supporting that HGF is a molecular predictor of recurrence The expression of HGF is lower than that of c-met in the low grade meningiomas, supporting that c-met may have a biological role in the low grade meningioma. There is a high HGF expression and coexpression of HGF/c-met in high grade meningiomas.

HGF, hepatocyte growth factor; WHO, World Health Organization; RT-PCR, reverse transcription polymerase chain reaction; ELISA, enzyme-linked immunosorbent assay.

meningioma vascularity and anti-HGF monoclonal antibody caused little inhibition of the extract-induced effects on endothelial cells. These findings suggest that antiangiogetic therapy to target HGF/SF in meningioma may be redundant. The concentration of HGF was not related to a higher malignancy grade or to meningioma vascularity in their study, which disagrees with the results of our study. HGF and the coexpression of HGF/c-met were expressed in the high grade meningiomas (grade II and III) in the present study, and this supports the theory that HGF may play a critical role in the progression of meningima, as occurs in glioma.[15,18] These different observations may be ascribed to the limited number of samples and different investigational methods such as enzyme-linked immunosorbent assay, immunohistochemistry or RT-PCR. The results of the previous studies are summarized in Table 2.[16,18,21-23]

Based on our results, HGF could represent not only a reliable predictor for recurrence of meningiomas but could also be an attractive target for new therapeutic schemes because its inhibition could produce antiproliferative effects. These enhance the response to chemotherapy and radiotherapy.[24,25] Therapeutic attempts could be made to block the HGF receptors as a potential adjuvant treatment. These results suggest that the measurement of HGF may be used as a predictive factor for planning therapeutic strategies for meningiomas due to the fact that HGF inhibits drug-induced cytotoxicity and apoptosis in experimental neoplasms that were treated by radiation or chemotherapy. One experimental approach has been to transfer the *HGF/NK2* gene to human glioma cells; this natural blocker of HGF activity decreases tumor activity and the overexpression of HGF.[26,27]

We found that the expression of HGF and the coexpression of HGF/c-met mRNAs were associated with an increased histological grade of meningiomas, and HGF was especially associated with recurrence. Although a few recurrent cases were included in the present study, HGF may be a promising independent prognostic marker for meningiomas and treatment targeted to HGF need to be investigated in the near future.

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