Expression of macrophage migration inhibitory factor is associated with enhanced angiogenesis and advanced stage in gastric carcinomas

Chia-Tung Shun, Jaw-Town Lin, Shih-Pei Huang, Min-Tsan Lin, Ming-Shiang Wu

INTRODUCTION

Despite its decline in incidence, gastric carcinoma (GC) remains the second most frequent cancer in the world[1]. In some countries, especially those of the Far East such as China and Japan, GC is the leading cause of cancer death. The prognosis of GC is dismal because the majority of cases are found to have advanced disease at the time of diagnosis. To improve the diagnosis and management of GC, a better understanding of the pathogenesis and tumor biology is mandatory. In the multistage model of gastric carcinogenesis, chronic inflammation is a prerequisite for the development of GC. Accordingly, factors involved in initiation and regulation of the inflammatory process play an essential role in gastric carcinogenesis. In this regard, genetic and environmental forces interact in the transition from gastritis, metaplasia, to dysplasia and cancer. Previous studies have pointed out that environmental factors such as dietary habits, cigarette smoking, and Helicobacter pylori (H pylori) infection are associated with risks of GC. Furthermore, genetic abnormalities including genomic instabilities and alterations of p53 tumor suppressor gene are involved in the evolution from gastritis to GC[2].

Cytokines are crucial mediators of inflammatory and immune responses that may contribute to multiple aspects of carcinogenesis. Macrophage migration inhibitory factor (MIF) is a unique cytokine that attracts much attention due to its pluripotent property[3]. MIF was first identified as a T-cell-derived lymphokine[4,5]. In addition to its original ability to inhibit the migration of macrophages, MIF exhibits a broad range of immunostimulatory and proinflammatory activities[6]. Intriguingly, MIF could also be produced by a variety of mesenchymal, parenchymal and epithelial cell types, indicating its potentials beyond the immune system[7].

MIF may contribute to the progression and enhanced angiogenesis in a substantial portion of GCs.

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Key words: Gastric cancer; H pylori; Angiogenesis

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Abstract

AIM: Macrophage migration inhibitory factor (MIF) was reported to inactivate p53 and play an essential role in the growth and angiogenesis of tumors that arise at sites of chronic inflammation. Gastric inflammation is a prerequisite for the development of gastric carcinoma (GC), which has recently been linked to Helicobacter pylori (H pylori) infection. This study aimed to investigate clinicopathological significance of MIF expression in GCs.

METHODS: We selected 90 consecutive patients with GCs for investigation of the relation among MIF status, clinicopathological parameters, p53 expression and angiogenesis. MIF and p53 expression was assessed by immunohistochemistry as positive and negative groups. Tumor vascularity was evaluated by counting microvessel density on anti-CD34 stained sections. Expression status of MIF was correlated with determined clinicopathological data, p53 immunoreactivity and microvessel counts.

RESULTS: Strong immunostainings of MIF were observed in the cytoplasm of cancerous cells in 40% (36/90) of cases but not in normal or metastatic epithelia. There was no statistically significant correlation between MIF expression and age, gender, H pylori infection, tumor location, histological subtypes, lymph node metastasis or p53 expression. Early GC less frequently overexpressed MIF as compared to advanced GCs (4/20 vs 32/70, P = 0.04). A remarkably increased microvessel count was noted in GCs with MIF expression than those without MIF expression (55.1±30.1 vs 31.3±28.8, P = 0.0001).

CONCLUSION: Our results suggest that expression of MIF may contribute to the progression and enhanced angiogenesis in a substantial portion of GCs.

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Background: The prognosis of gastric carcinoma (GC) is discouraging due to late diagnosis and advanced disease at the time of diagnosis. A better understanding of the pathogenesis and tumor biology is crucial for improving the diagnosis and management of GC. In the multistage model of gastric carcinogenesis, chronic inflammation is a prerequisite for the development of GC. Inflammation and cell growth are dependent on the balance of pro- and anti-inflammatory factors. Cytokines are crucial mediators of inflammatory and immune responses that may contribute to multiple aspects of carcinogenesis. Macrophage migration inhibitory factor (MIF) is a unique cytokine that attracts much attention due to its pluripotent property[3]. MIF was first identified as a T-cell-derived lymphokine[4,5]. In addition to its original ability to inhibit the migration of macrophages, MIF exhibits a broad range of immunostimulatory and proinflammatory activities[6]. Intriguingly, MIF could also be produced by a variety of mesenchymal, parenchymal and epithelial cell types, indicating its potentials beyond the immune system[7].

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A number of recent studies have shown that MIF participates in the regulation of cell proliferation and differentiation, and is related to septic shock, chronic inflammatory and autoimmune disease[6,7]. In the context of tumorigenesis, overexpression of MIF has been observed in prostate[31], lung[10,13], skin[9], pituitary[16], brain[14], breast[13], liver[15], and colon tumors[7]. Furthermore, Hudson et al[30], showed that p53, the guardian of genome, can be functionally inactivated by MIF. This finding has helped to establish a link between inflammation and tumorigenesis in view of the central role of p53 in tumor growth and tumor-associated angiogenesis. Collectively, inhibition of p53 by MIF may be critical for the development of tumors that arise at sites of chronic inflammation, such as colon cancer in ulcerative colitis, and GC in H pylori infection[29].

Recently, Maaset et al[31], have suggested that MIF was constitutively expressed at the messenger RNA and protein level by gastric epithelial cell lines. Moreover, Huang et al[30], have demonstrated that MIF was an important mediator in the pathogenesis of gastric inflammation in rats. However, no study of MIF expression in GC has been performed. We therefore aimed to evaluate by immunohistochemistry the prevalence of MIF expression in a series of GCs and to correlate this expression with clinicopathological parameters, p53 immunoreactivity and microvessel counts.

MATERIALS AND METHODS

Patients and tissue specimens

This study was carried out on 90 consecutive cases that were selected from a series of GCs with complete clinicopathological parameters[12,32]. Age and gender were recorded from medical records. Routine hematoxylin-eosin staining on sections of GC was performed to determine the depth of cancer invasion, histological type. Modified Giemsa stains were used to identify status of H pylori infection. The extent of tumor invasion was further divided into early and advanced GC according to the criteria proposed by the Japanese Research Society for Gastric Cancer[34]. A GC is defined as early GC if the tumor is limited to the mucosa or the submucosa and defined as advanced GC if the tumor invades into the muscularis propria[35]. Histological types were classified into intestinal or diffuse type according to Lauren’s criteria[33]. Tumor location was defined as non-cardiac for those at the antrum and/or body and cardiac for GC located at cardia.

Immunohistochemical staining of MIF and p53 proteins Formalin-fixed and paraffin-embedded tissues were cut into 5-µm-thick sections, deparaffinized, and then rehydrated. Antigen retrieval was performed by microwave method and endogenous peroxidase activity was blocked with 3% H2O2 in Tris-buffered saline (TBS). Non-specific binding was blocked with 5% rabbit serum (DAKO, Glostrup, Denmark) in TBS. The sections were incubated with primary antibody against MIF (1:400, R&D System Inc., USA) or anti-p53 mouse monoclonal antibody DO-1 (IgG2α class, 1:20 dilution, Novocastra Laboratories Ltd, Tyne, UK) in TBS containing 2% rabbit serum and 1% bovine serum albumin overnight. This was followed by incubation with a biotinylated secondary antibody, peroxidase-conjugated streptavidin and then colorization by using dianaminobenzidine as chromogen to visualize the activity. The negative controls were performed by incubating samples without the primary antibodies.

The extent of MIF expression was classified into negative and positive immunoreactivity, defined as positive cytoplasmic staining less than 10%, and more than 10% in tumor cells, respectively. In grading of p53 expression, only nuclear localization of immunoreactivity was evaluated. The extent of nuclear p53 protein was classified into low and high nuclear immunoreactivity, defined as positive nuclei less than 10% and more than 10% in tumor cells, respectively. The immunohistochemical analysis was performed without the knowledge of the clinicopathological features of the patients.

Microvessel density (MVD)

Vascularity was defined as the number of vessels per field counted in the area of highest vascular density stained by anti-CD34 antibody[36]. After antigen retrieval, endogenous peroxidase was blocked with 3% hydrogen peroxide. Each section was incubated with non-immune horse serum. The sections were incubated in an anti-CD34 monoclonal antibody (Santa Cruz Biotechnology, Inc., Santa Cruz, CA) to recognize endothelium-specific antigen CD34. The sections were incubated with biotinylated secondary antibodies followed by peroxidase-conjugated streptavidin complex. The peroxidase activity was visualized with dianaminobenzidine as the chromogen. At low power field (×40), the tissue sections were screened and five areas with the most intense neovascularization (hot spots) were selected. The separate areas of microvessels were counted at high power field (×200) and the mean count of the five areas was taken as the Microvessel density (MVD) to stand for tumor vascularity.

Statistical analysis

All statistical calculations were performed by SPSS for Windows software (version 10.0). Age and MVD were expressed as mean±SD and compared by Student’s t test. Categorical data were analyzed by Fisher’s exact or χ2 tests when appropriate. A P value (two-tailed) less than 0.05 was considered statistically significant.

RESULTS

A total of 90 GCs were enrolled. The demographic and clinicopathological data were listed in Table 1. MIF was not expressed in the normal gastric mucosa or metaplastic cells that were located in the tumors adjacent to the stomach. In stromal cells, the cytoplasm of macrophages was vividly stained. The relationships between MIF expression and clinicopathological profiles were summarized in Table 1. MIF expression was not correlated with the parameters such as age, gender,
**DISCUSSION**

This study investigated MIF expression in a series of human GCs. By immunohistochemistry, we clearly demonstrated widespread cytoplasmic localization in 40% of GCs as opposed to lack of expression in normal and metaplastic mucosa. In contrast to previous studies showing that MIF was expressed in gastric epithelia,[10,31] we found no or very weak staining of MIF in surface epithelial cells and 60% of GCs. This discrepancy might be partially attributed to heterogeneity of methods for analyzing MIF in different studies. In addition, it is noteworthy that macrophages located directly beneath the epithelial cells demonstrated strong immunostainings of MIF. Such staining might also interfere the interpretation of MIF expression. Taken together, our results indicate that overexpression of MIF, similar to those reported in other carcinomas,[8-12], is observed in a substantial portion of GCs.

Thus far, MIF expression has been studied for a variety of carcinomas, including prostate, lung, breast, liver and colon cancers.[13-17]. These studies consistently showed the overexpression of MIF in carcinomas compared with benign lesions. Except for a study showing intranuclear expression of MIF in 80% of lung cancers[10], most studies including ours have reported cytoplasmic stainings of MIF in cancer cells. Collectively, the aberrant production of MIF in different tumor types suggests the potential involvement of MIF in carcinogenesis.

Although traditionally considered to be a cytokine,[4-6] the important and previously unappreciated role of MIF in tumorigenesis has recently attracted much attention.[22,28]. It is now well known that MIF is related to various events in carcinogenesis such as cellular proliferation, migration, and angiogenesis.[7]. By blocking MIF with anti-MIF antibody or anti-sense plasmid transfection, tumor cell growth and migration was suppressed[19-21,25]. Moreover, enhanced tumor growth and associated angiogenesis was observed in MIF transgenic mice.[30]. The investigations of mRNA and protein expression in specimens of melanoma, non-small cell lung cancer and hepatocellular carcinoma also confirmed that tumor angiogenesis was correlated with MIF levels[9,15,21]. In keeping with these observations, we found a positive correlation between MVD and MIF expression in GCs. However, the mechanisms of MIF in promoting angiogenesis remain obscure. Among the various angiogenic inducers and inhibitors identified to date, angiogenic factor such as interleukin-8, vascular endothelial growth factor and angiogenic CXC chemokine have been reported to positively correlate with MIF expression[14,24,25]. Whether similar mechanisms underlying the increased angiogenesis in GCs and the relationship between MIF expression and angiogenic factors remains to be further clarified.

Although many in vitro studies have highlighted the critical role of MIF in tumor progression and angiogenesis,[19-22] few data regarding MIF expression in the different clinicopathological profiles of malignancies remain.[8-11]. We detected a higher frequency of MIF expression in advanced GCs compared with early GCs. Our results indicate that MIF could be upregulated in gastric epithelial cells during GC progression and that it could be relevant to the
acquisition of deeper depth of invasion. This is in agreement with data demonstrating that increased MIF expression is significantly correlated with an aggressive phenotype in prostate cancer and melanoma[8,9]. Previous studies of other tumor types have yielded conflicting results concerning the association between MIF expression and histological grade, nodal metastasis and prognosis[13-17]. Our study revealed that MIF expression in GCs did not significantly differ between histological subtypes, tumor location, and lymph node metastases. Enhancement of MIF has been reported to be associated with minimal nodal spread and a favorable prognosis in breast cancer[13]. In colon cancers, Legendre et al[17], have reported that MIF reactivity in connective tumor tissues might determine the prognosis; although the expression in epithelial tumor tissues showed no significance for Duke grade and prognosis. In contrast to most studies showing that MIF was present in the cytoplasm of cancer cells, intranuclear staining of MIF was demonstrated in lung cancer and could predict a good prognosis[8,14]. However, an aggressive phenotype characterized by the presence of dedifferentiation and metastasis was found in prostate cancers[8,11]. We speculated that tissue-specific effect and expression site of MIF might contribute to these discrepant observations. Obviously, the relationship between MIF expression and clinicopathological characteristics of malignancies has to be confirmed in different tumor types.

Recent epidemiological studies have confirmed that *H pylori* infection is associated with an increased risk of GC. As both MIF and *H pylori* are found at sites of inflammation, it is intriguing to investigate whether *H pylori* could influence the status of MIF expression. No significant association was found between *H pylori* infection and MIF expression in the current study. Since our results implicate that the role of MIF predominated in tumor progression, these observations appear to be consistent with the notion that *H pylori* participates in gastric carcinogenesis mainly in the initiation stage[8,9]. Nevertheless, further in-depth studies of the aberrant expression of MIF in *in vitro* or *in vivo* models of GCs and *H pylori* infection are needed.

p53 plays a pivotal role via different route and control multiple downstream pathways in tumorigenesis. Prompted by studies on experimental cell lines and animal models suggesting that MIF could inactivate p53[18,20], we investigated a possible association between p53 and MIF expression. We did not find a significant correlation between p53 nuclear immunopositivities and MIF expression. It is noteworthy that this did not mean that the function of p53 was not related to MIF since p53 immunostainings are not equal to its dysfunction. Recently, Hudson et al[18], have shown that MIF is capable of inhibiting several p53 function despite there being no obvious difference in p53 protein localization or protein abundance with MIF treatment. Further studies are mandatory to elucidate the interaction between p53 and MIF.

In conclusion, immunohistochemical expression of MIF and its clinicopathological significance were assessed in a series of GCs. Our work provides evidence-linking MIF with tumor progression and enhanced angiogenesis in gastric carcinogenesis, but the mechanisms of the aberrant expression in GCs and how MIF acts to promote tumorigenesis remains to be further elucidated.

REFERENCES

1. Correa P. Human gastric carcinogenesis: a multistep and multifactorial process—First American Cancer Society Award Lecture on Cancer Epidemiology and Prevention. Cancer Res 1992; 52: 6735-6470
2. Tahara E, Semb S, Tahara H. Molecular biological observations in gastric cancer. Semin Oncol 1996; 23: 307-315
3. Nishihira J. Macrophage migration inhibitory factor (MIF): its essential role in the immune system and cell growth. J Interferon Cytokine Res 2000; 20: 751-762
4. David JR. Delayed hypersensitivity in vitro: its mediation by cell-free substances formed by lymphoid cell-antigen interaction. Proc Natl Acad Sci USA 1966; 56: 72-77
5. Bloom BR, Bennett B. Mechanism of a reaction in vitro associated with delayed-type hypersensitivity. Science 1966; 153: 80-82
6. Bucala R. MIF rediscovered: cytokine, pituitary hormone, and glucocorticoid-induced regulator of the immune response. FASEB J 1996; 10: 1607-1613
7. Lue H, Kleemann R, Calandra T, Roger T, Bernhagen J. Macrophage migration inhibitory factor (MIF): mechanisms of action and role in disease. Microbes Infect 2002; 4: 449-460
8. Meyer-Siegler K, Hudson PB. Enhanced expression of macrophage migration inhibitory factor in prostatic adenocarcinoma metastases. Urology 1996; 48: 448-452
9. Shimizu T, Abe R, Nakamura H, Ohkawara A, Suzuki M, Nishihira J. High expression of macrophage migration inhibitory factor in human melanoma cells and its role in tumor cell growth and angiogenesis. Biochem Biophys Res Commun 1999; 264: 751-758
10. Kaminura A, Kamachi M, Nishihira J, Ogura S, Isobe H, Dosaka-Akita H, Ogata A, Shindoh M, Obuchi T, Kawakami Y. Intracellular distribution of macrophage migration inhibitory factor predicts the prognosis of patients with adenocarcinoma of the lung. Cancer 2000; 89: 334-341
11. del Vecchio MT, Tripodi SA, Arcuri F, Pergola L, Hako L, Vatti R, Cintorino M. Macrophage migration inhibitory factor in prostatic adenocarcinoma: correlation with tumor grading and combination endocrine treatment related changes. Prostate 2000; 45: 51-57
12. Akbar SM, Abe M, Murakami H, Tanimoto K, Kumagi T, Yamashita Y, Michitaka K, Horiike N, Onji M. Macrophage migration inhibitory factor in hepatocellular carcinoma and liver cirrhosis: relevance to pathogenesis. Cancer Lett 2001; 171: 125-132
13. Bando H, Matsumoto G, Bando M, Muta M, Ogawa T, Funata N, Nishihira J, Koike M, Toi M. Expression of macrophage migration inhibitory factor in human breast cancer: association with nodal spread. Jpn J Cancer Res 2002; 93: 389-396
14. Munaut C, Boniver J, Foidart JM, Deprez M. Macrophage migration inhibitory factor (MIF) expression in human glioblastomas correlates with vascular endothelial growth factor (VEGF) expression. Neuropathol Appl Neurobiol 2002; 28: 452-460
15. Tomiyasu M, Yoshino I, Suemitsu R, Okamoto T, Sugimachi K. Quantification of macrophage migration inhibitory factor mRNA expression in non-small cell lung cancer tissues and its clinical significance. Clin Cancer Res 2003; 8: 3755-3760
16. Pyle ME, Korbonits M, Guerguiev M, Jordan S, Kola B, Morris DC, Meinhardt A, Powell MP, Claret FX, Zhang Q, Metz C, Bucala R, Grossman AB. Macrophage migration inhibitory factor expression is increased in pituitary adenoma cell nuclei. J Endocrinol 2003; 176: 103-110
17. Legendre H, Decaestecker C, Nagy N, Hendliss A, Schuring MP, Salmon I, Gabius HJ, Pector JC, Kiss R. Prognostic values of galectin-3 and the macrophage migration inhibitory factor (MIF) in human colorectal cancers. Mod Pathol 2003; 16: 491-504
18. Hudson JD, Shoaiib MA, Maestro R, Camero A, Hannon GJ, et al.
Beach DH. A proinflammatory cytokine inhibits p53 tumor suppressor activity. J Exp Med 1999; 190: 1375-1382

Takahashi N, Nishihira J, Sato Y, Kondo M, Ogawa H, Ohshima T, Une Y, Todo S. Involvement of macrophage migration inhibitory factor (MIF) in the mechanism of tumor cell growth. Mol Med 1998; 5: 181-191

Chesney J, Metz C, Bacher M, Peng T, Meinhardt A, Bucala R. An essential role for macrophage migration inhibitory factor (MIF) in angiogenesis and the growth of a murine lymphoma. Mol Med 1999; 4: 707-714

Ogawa H, Nishihira J, Sato Y, Kondo M, Takahashi N, Oshima T, Todo S. An antibody for macrophage migration inhibitory factor suppresses tumour growth and inhibits tumour-associated angiogenesis. Cytokine 2000; 12: 309-314

White ES, Strom SR, Wys NL, Arenberg DA. Non-small cell lung cancer cells induce monocytes to increase expression of angiogenic activity. J Immunol 2001; 166: 7549-7555

Bin Q, Johnson BD, Schauer DW, Casper JT, Orentas RJ. Production of macrophage migration inhibitory factor by human and murine neuroblastoma. Tumour Biol 2002; 23: 123-129

White ES, Flaherty KR, Carskadon S, Brant A, Iannettoni MD, Yee J, Orringer MB, Arenberg DA. Macrophage migration inhibitory factor and CXC chemokine expression in non-small cell lung cancer: role in angiogenesis and prognosis. Clin Cancer Res 2003; 9: 853-860

Ren Y, Tsui HT, Poon RT, Ng IO, Li Z, Chen Y, Jiang G, Lau C, Yu WC, Bacher M, Fan ST. Macrophage migration inhibitory factor: roles in regulating tumor cell migration and expression of angiogenic factors in hepatocellular carcinoma. Int J Cancer 2003; 107: 22-29

Bacher M, Schrader J, Thompson N, Kuschela K, Gemsa D, Waebler G, Schlegel J. Up-regulation of macrophage migration inhibitory factor gene and protein expression in glial tumor cells during hypoxic and hypoglycemic stress indicates a critical role for angiogenesis in glioblastoma multiforme. Ant J Pathol 2003; 162: 11-17

Mitchell RA, Bucala R. Tumor growth-promoting properties of macrophage migration inhibitory factor (MIF). Semin Cancer Biol 2000; 10: 359-366

Nishihira J, Ishibashi T, Fukushima T, Sun B, Sato Y, Todo S. Macrophage migration inhibitory factor (MIF): Its potential role in tumor growth and tumor-associated angiogenesis. Ann N Y Acad Sci 2003; 995: 171-182

Fingerle-Rowson G, Petrenko O, Metz CN, Forsthuber TG, Mitchell R, Huss R, Moll U, Muller W, Bucala R. The p53-dependent effects of macrophage migration inhibitory factor revealed by gene targeting. Proc Natl Acad Sci USA 2003; 100: 9354-9359

Maaser C, Eckmann L, Paesold G, Kim HS, Kagnoff MF. Ubiquitous production of macrophage migration inhibitory factor by human gastric and intestinal epithelium. Gastroenterology 2002; 122: 667-680

Huang XR, Chun Hui CW, Chen YX, Wong BC, Fung PC, Metz C, Cho CH, Hui WM, Bucala R, Lam SK, Lan HY. Macrophage migration inhibitory factor is an important mediator in the pathogenesis of gastric inflammation in rats. Gastroenterology 2001; 121: 619-630

Wu MS, Shun CT, Wu CC, Hsu TY, Lin MT, Chang MC, Wang HP, Lin JT. Epstein-Barr virus-associated gastric carcinomas: relation to H pylori infection and genetic alterations. Gastroenterology 2000; 118: 1031-1038

Huang SP, Wu MS, Shun CT, Wang HP, Lin JT. Tumor angiogenesis increases with nuclear p53 accumulation in gastric carcinoma. Hepatogastroenterology 2002; 49: 1453-1456

Murakami T. Pathomorphological diagnosis: definition and gross classification of early gastric cancer. Gann Monogr 1971; 11: 53-55

Lauren P. The two histological main types of gastric carcinoma diffuse and so-called intestinal type carcinoma. an attempt at a histo-clinical classification. Acta Pathol Microbiol Scand 1965; 64: 31-49