Combined upregulation of matrix metalloproteinase-1 and proteinase-activated receptor-1 predicts unfavorable prognosis in human nasopharyngeal carcinoma

Rui Yang1
Yu Xu2
Peizhong Li3
Xin Zhang2
Junying Wang2
Dongsheng Gu2
Yao Wang3

1State Key Laboratory of Cancer Biology, Cell Engineering Research Center and Department of Cell Biology, Department of Clinical Nursing, School of Nursing, The Fourth Military Medical University, Xi’an, People’s Republic of China; 2Department of Otorhinolaryngology, Huai’an First People’s Hospital, Nanjing Medical University, Huai’an, Jiangsu, People’s Republic of China; 3Pharmaceutical Preparation Section, Huai’an First People’s Hospital, Nanjing Medical University, Huai’an, Jiangsu, People’s Republic of China

Background: The upregulation of matrix metalloproteinase-1 (MMP-1) has been demonstrated to be correlated with lymph node metastasis of nasopharyngeal carcinoma (NPC), while the activation of protease-activated receptor-1 (PAR-1) mediates proliferation and invasion of NPC cells. The present study investigated the clinical significance of the coexpression of MMP-1 and PAR-1 in NPC patients in determining the prognosis.

Methods: Immunohistochemistry was performed to detect the expression of MMP-1 and PAR-1 in tumor tissue samples from 266 NPC patients.

Results: Overexpression of MMP-1 and PAR-1 proteins were, respectively, detected in 190 (71.43%) and 182 (68.42%) of the 266 NPC patients. In addition, the combined MMP-1 and PAR-1 expression was significantly associated with advanced T-stage (P = 0.01), advanced clinical stage (P = 0.002), positive recurrence (P = 0.01), and metastatic status (P = 0.01) of NPC. Moreover, the overall survival in NPC patients with MMP-1 and PAR-1 dual overexpression was significantly shorter than in those with dual low expression (P < 0.001). Furthermore, the multivariate analyses indicated that the combined MMP-1 and PAR-1 overexpression was an independent prognostic factor for overall survival (P = 0.001) in NPC patients, but the upregulation of MMP-1 and PAR-1 alone was, in each case, not an independent prognostic factor for this disease.

Conclusion: Our data provide convincing evidence, for the first time, that the activation of the MMP-1 and PAR-1 axis may be involved in the tumorigenesis and progression of NPC. The upregulation of MMP-1 in combination with PAR-1 overexpression is an unfavorable prognostic marker for NPC and might offer the possibility of future therapeutic targets.

Keywords: MMP-1, PAR-1, nasopharyngeal carcinoma, coexpression, prognosis

Introduction
Nasopharyngeal carcinoma (NPC) is one of the most common malignant diseases, with a high prevalence in Southern China, Southeast Asia, and North Africa. Worldwide, NPC accounts for 80,000 new cases and 50,000 deaths annually, predominantly in men. NPC is an Epstein-Barr virus (EBV)-related cancer and differs from other head and neck cancers in its etiology, epidemiology, and potential therapeutic options. Generally, enlarged lymph nodes in the neck region are the first sign of NPC; however, neck biopsy or neck dissection is not recommended, as this may reduce cure probability. The majority (75%–90%) of newly diagnosed NPC patients have locoregionally advanced disease, commonly with cervical nodal metastases.
Currently, the standard of care for NPC patients consists of concurrent chemoradiotherapy with cisplatin-based regimens, generally followed by adjuvant chemotherapy. This treatment approach leads to cure for the vast majority of patients, with 3-year disease-free and overall survival rates of approximately 70% and 80%, respectively. Despite cure for the majority of the patients, it is still a challenge to prevent the disease relapse, to treat the patients with refractory or metastatic NPC, and to manage the long-term toxicities. Thus, there is an urgent need to identify the valuable factors for early diagnosis, prognosis, and novel therapeutic strategies.

Matrix metalloproteinases (MMPs) comprise a closely related family of 28 zinc-dependent endopeptidases that cleave extracellular matrix (ECM) proteins during tissue remodeling processes, such as wound healing, angiogenesis, and tumor invasion. Among MMPs, MMP-1, together with MMP-8 and MMP-13, is known as the interstitial collagenase and is capable of initiating the degradation of fibrillar-type collagens by cleaving at the N-terminus. MMP-1 presents specific substrates for collagens I, II, III, VII, VIII, and X, and for proteoglycans. It has been identified as one of the most highly upregulated proteins in various cancers. In particular, tumor expression of MMP-1 is associated with poor prognosis in malignant melanoma, breast cancer, ovarian cancer, colorectal carcinoma, pancreatic cancer, and gastric cancer. Recent studies have demonstrated that the collagenase activity of MMP-1 may be associated with tumor cell invasion and increased angiogenesis in xenograft models of malignant melanoma, breast cancer, and prostate cancer. In NPC, Lu et al showed clearly that the amounts of transcripts, proteins, and enzyme activities of MMP-1 were increased in cells expressing EBV proteins, suggesting that these viral proteins may be capable of regulating MMP-1 and may provide clues for the role of EBV in NPC progression; Ben Nasr et al indicated that the expression of MMP-1 may be correlated with lymph node metastasis in NPC patients. Although the collagenolytic activity of MMP-1 may contribute to the tumor progression of NPC, its prognostic value in this carcinoma remains largely undefined.

Recently, a novel MMP-1 signaling axis (through activation of the protease-activated receptor [PAR]-1 to promote tumorigenesis and tumor invasion) has been identified in various cancers, such as breast cancer, epithelial ovarian cancer, esophageal squamous cell carcinoma, glioma, and hepatocellular carcinoma. The PARs are known as the cellular seven transmembrane G protein-coupled receptors (GPCRs) for thrombin. Four different PARs have been identified: PAR-1, PAR-2, PAR-3, and PAR-4. PARs are widely expressed in vascular and extravascular tissues and are involved in responses to vascular injury and in the regulation of inflammation. PAR-1 and PAR-3 are activated by thrombin, PAR-2 is activated by tryptase or trypsin, and PAR-4 is activated by both thrombin and tryptase or trypsin. Among the PARs, the abnormal expression of PAR-1 has been demonstrated to be associated with the metastatic potentials of various malignancies, including breast cancer, prostate cancer, and melanoma. In particular, Zhu et al indicated that the activation of PAR-1 may mediate the proliferation and invasion of NPC cells. Since the MMP-1/PAR-1 signal transduction axis facilitates tumor invasion, angiogenesis, and metastasis by inducing the expression of the genes associated with cell adhesion, invasion, and survival, it is of great significance to explore the expression and prognostic value of MMP-1 and PAR-1 in NPC. However, to date, there has been no investigation of the clinicopathologic relevance of combined MMP-1 and PAR-1 expression in NPC tissues. Therefore, the aim of the present study was to evaluate the potential association of the coexpression of MMP-1 and PAR-1 in NPC tissues with clinicopathologic findings and with postresectional survival, by an immunohistochemical analysis.

Materials and methods
Patients and tissue samples
The study was approved by the Research Ethics Committee of the Ministry of Public Health of the People’s Republic of China. Informed consent was obtained from all of the patients.

A total of 266 archival formalin-fixed, paraffin-embedded NPC specimens and 100 noncancerous nasopharyngeal specimens were obtained from Huai’an First People’s Hospital, Nanjing Medical University, People’s Republic of China during 1996–2006. In the 266 NPC group of patients, there were 166 males and 100 females, with age ranging from 16 to 80 years (median, 48 years). None of the patients recruited in this study had chemotherapy or radiotherapy before the surgery. Clinical information was obtained by reviewing the medical record of radiographic images, by telephone or written correspondence, and by review of death certificates. All specimens had a confirmed pathological diagnosis and were staged according to the 1992 NPC staging system of the People’s Republic of China. The clinical characteristics of these patients are summarized in Table 1.

For the analysis of survival and follow up, the date of surgery was used to represent the beginning of the
follow-up period. All the patients who died from diseases other than NPC or from unexpected events were excluded from the case collection. The study follow-up period terminated at March 8, 2012. The median follow-up period was 46 months (range, 3–126 months). Treatment modalities after relapse were given according to a uniform guideline, as described.31

**Immunohistochemistry analysis**

The expression patterns of the MMP-1 and PAR-1 proteins in the 266 NPC specimens and 100 noncancerous nasopharyngeal specimens were detected by immunohistochemical staining. In brief, all tissue specimens were retrieved and cut into 4 µm sections and then, mounted on precoated slides. After deparaffinizing in xylene (Chemical Industry Co., Ltd., Shenzhen, People’s Republic of China) and washing in a graded series of ethanol (Chemical Industry Co., Ltd.), the sections were submerged into ethylenediaminetetraacetic acid (EDTA) antigenic retrieval buffer (Chemical Industry Co., Ltd.) and microwaved for antigenic retrieval. The slides were incubated with primary antibodies raised against MMP-1 (1:1000 dilution) (MMP-1 [3B6] Antibody; #sc-21731, Santa Cruz Biotechnology, Inc, Dallas, TX, USA) and against PAR-1 (1:1000 dilution) (Antibody; #sc-33732, Santa Cruz Biotechnology, Inc). All incubations with primary antibodies were carried out overnight at 4°C. After washing in tris(hydroxymethyl) aminomethane (Tris)-buffered saline (TBS) (Sigma Aldrich Corp, St Louis, MO, USA), the tissue sections were treated with biotinylated anti-rabbit secondary antibody (Antibody; #sc-2775, Santa Cruz Biotechnology, Inc), followed by further incubation with streptavidin–horseradish peroxidase complex (Life Technologies Corp, Carlsbad, CA, USA). The tissue sections were immersed in 3-amino-9-ethyl carbazole (Chemical Industry Co., Ltd.) and counterstained with 10% Mayer’s hematoxylin (Chemical Industry Co., Ltd.), dehydrated, and mounted in Crystal Mount™ Aqueous Mounting Medium (Chemical Industry Co., Ltd). In each immunohistochemistry run, noncancerous nasopharyngeal specimens were used as control tissues, and omission of the primary antibody served as a negative control. All the tissue samples were stained at one time.

Following the hematoxylin counterstaining, immunostaining was scored by two independent observers who were
blinded to the clinicopathological parameters and clinical outcomes of the patients. The scores of the two observers were compared, and in the event of a discrepant score, the specimen was reexamined by both pathologists to achieve a consensus score. The number of positive-staining cells showing immunoreactivity on the cell membrane and/or cytoplasm (for MMP-1) and cytoplasm (for PAR-1) in ten representative microscopic fields was counted, and the percentage of positive cells was calculated. The frequency of MMP-1 and PAR-1 immunoreactivity in tissue sections was evaluated as negative (0), when no positive cells were observed within the tumor; as weak (1), when <30% of the tumor cells were positive; moderate (2), when 30% to 60% of the tumor cells were positive; and strong (3), when >60% of tumor cells were positive. The intensity of staining was evaluated as 0, 1, 2, and 3 for no staining, weak staining, medium staining, and strong staining, respectively. The immunohistochemical scores were determined as the sum of the frequency and intensity scores for the tumor cells. The cutoff values for the immunohistochemical scores of MMP-1 and PAR-1 proteins were chosen on the basis of a measure of heterogeneity, with the logrank test statistic, with respect to overall survival. An optimal cutoff value was identified. An immunohistochemical score of ≥4 was used to classify tumors with high expression, while a <4 immunohistochemical score classified tumors with low expression of MMP-1 or PAR-1 antigens.

**Statistical analysis**

SPSS for Windows version 16.0 (SPSS Inc, Chicago, IL, USA) and SAS 9.1 (SAS Institute, Cary, NC, USA) were used for statistical analysis. Continuous variables were expressed as $\bar{X} \pm s$. Associations between the expression of MMP-1 and/or PAR-1 and clinicopathological parameters were assessed using a Chi-square test. The Spearman rank correlation test was used to analyze the correlation between the MMP-1 expression level and the PAR-1 expression level. Survival curves were plotted by Kaplan–Meier analysis and compared by the logrank test. Cox regression analysis was performed to assess the significance of various variables for survival. Differences were considered statistically significant when the $P$-value was less than 0.05.

**Results**

**Upregulation of MMP-1 and PAR-1 in human NPC**

The expression patterns and cellular distribution of MMP-1 and PAR-1 in 266 specimens of patients with NPC and 100 noncancerous nasopharyngeal tissues were examined using immunohistochemical staining. As shown in Figure 1, the cell membrane and/or cytoplasm of most tumor cells in the NPC sections stained intensely with MMP-1 antibody (Figure 1A), while negative immunostaining was observed in all noncancerous nasopharyngeal tissues (Figure 1B). High MMP-1 expression was observed in tumor cells of 71.43% (190/266) of the NPC patients. For PAR-1, positive immunostaining was observed in the cytoplasm of the tumor cells (Figure 1C). In contrast, little or no expression of PAR-1 was observed in the noncancerous nasopharyngeal tissues (Figure 1D). High PAR-1 expression was observed in tumor cells of 68.42% (182/266) of the NPC patients. In particular, high MMP-1 expression was positively correlated with high PAR-1 expression in the tissue from patients with NPC ($r = 0.86$) ($P < 0.0001$) (Table 2).

**Association of MMP-1 and/or PAR-1 protein expression with the clinicopathological characteristics of human NPC**

Table 1 summarizes the association of MMP-1 and/or PAR-1 protein expression in the 266 NPC specimens, detected by immunohistochemical staining. Expression of MMP-1 was significantly associated with the T-stage ($P = 0.02$), clinical stage ($P = 0.008$), and metastatic status ($P = 0.01$). No significant association between MMP-1 expression and age, gender, N-stage, World Health Organization (WHO)
The association of MMP-1 and/or PAR-1 protein expression with the prognosis of human NPC was also evaluated. The 5-year overall survival rate of the cohort of 266 NPC patients was 66.17% (196/266). Kaplan–Meier survival analysis revealed that the NPC patients overexpressing both MMP-1 and PAR-1 proteins exhibited markedly poorer overall survival ($P = 0.01$) (Figure 2A and B). Regarding their combined expression, the overall survival in NPC patients with MMP-1 and PAR-1 dual overexpression was significantly shorter than those with dual low expression ($P < 0.001$) (Figure 2C).

Univariate Cox proportional hazard regression analysis revealed that high MMP-1 expression (hazard ratio [HR] = 5.796, 95% confidence interval [CI]: 0.826–12.013) ($P = 0.01$), high PAR-1 expression (HR = 5.282, 95% CI: 0.701–11.819) ($P = 0.01$), and MMP-1-high/PAR-1-high expression (HR = 13.882, 95% CI: 1.986–92.331) ($P < 0.001$) were significant predictive factors for poor prognosis in NPC patients. Other clinicopathologic parameters, including clinical stage (HR = 7.382, 95% CI: 1.031–16.613) ($P = 0.002$), recurrence (HR = 8.892, 95% CI: 1.021–18.656) ($P = 0.001$), and metastasis (HR = 8.788, 95% CI: 1.042–19.052) ($P = 0.001$), were also found to be prognostic predictors.

### Table 2 Correlations between MMP-1 and PAR-1 expression in nasopharyngeal carcinoma tissues

<table>
<thead>
<tr>
<th></th>
<th>High PAR-1 expression</th>
<th>Low PAR-1 expression</th>
<th>Spearman rank correlation coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>High MMP-1 expression</td>
<td>162 (85.26%)</td>
<td>28 (14.74%)</td>
<td>0.86</td>
</tr>
<tr>
<td>Low MMP-1 expression</td>
<td>20 (26.32%)</td>
<td>56 (73.68%)</td>
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</tbody>
</table>

Abbreviations: MMP, matrix metalloproteinases; PAR, protease-activated receptor.
Table 3 Univariate analysis of different prognostic variables in 266 nasopharyngeal carcinoma patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>Subset</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient gender</td>
<td>Male vs female</td>
<td>1.987</td>
<td>0.608–4.092</td>
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<tr>
<td>Patient age</td>
<td>&lt;48 vs ≥48</td>
<td>1.566</td>
<td>0.465–3.853</td>
<td>NS</td>
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<tr>
<td>Clinical stage</td>
<td>I–II vs III–IV</td>
<td>7.382</td>
<td>1.031–16.113</td>
<td>0.002</td>
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<td>T-stage</td>
<td>T1–T2 vs T3–T4</td>
<td>2.380</td>
<td>0.738–5.046</td>
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<td>N-stage</td>
<td>N0 vs N1–N3</td>
<td>1.778</td>
<td>0.732–4.028</td>
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<td>WHO</td>
<td>II vs III</td>
<td>1.458</td>
<td>0.689–3.076</td>
<td>NS</td>
</tr>
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<td>histological type</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recurrence</td>
<td>No vs yes</td>
<td>8.892</td>
<td>1.021–18.656</td>
<td>0.001</td>
</tr>
<tr>
<td>Metastasis</td>
<td>No vs yes</td>
<td>8.788</td>
<td>1.042–19.052</td>
<td>0.001</td>
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<tr>
<td>MMP-I</td>
<td>Low vs high</td>
<td>5.796</td>
<td>0.826–12.013</td>
<td>0.01</td>
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<tr>
<td>PAR-1</td>
<td>Low vs high</td>
<td>5.282</td>
<td>0.701–11.819</td>
<td>0.01</td>
</tr>
<tr>
<td>MMP-I/Par-1</td>
<td>MMP-I-high/Par-1-low vs MMP-I-low/Par-1-high</td>
<td>13.882</td>
<td>1.986–29.331</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Note: NS refers to the difference without statistical significance.

Abbreviations: CI, confidence interval; HR, hazard ratio; MMP, matrix metalloproteinases; PAR, protease-activated receptor; WHO, World Health Organization.

of overall survival in NPC patients (Table 3). Furthermore, multivariate Cox proportional hazards regression analysis indicated that combined MMP-1 and PAR-1 overexpression (HR = 9.167, 95% CI: 1.332–23.836) (P = 0.001), clinical stage (HR = 6.193, 95% CI: 1.011–13.392) (P = 0.006), recurrence (HR = 6.928, 95% CI: 0.922–13.556) (P = 0.005), and metastasis (HR = 6.893, 95% CI: 1.023–13.528) (P = 0.005) were independent prognostic factors for overall survival in NPC patients, but the upregulation of MMP-1 and PAR-1 alone was, in each case, not an independent prognostic factor for this disease (Table 4).

Discussion

NPC is an EBV-related cancer with a high metastatic potential compared to other head and neck cancers. There is a significant need for the identification of potential biomarkers to screen patients who are at the great risk of relapse after their primary treatment. In the present study, we analyzed the expression of MMP-1 and/or PAR-1 together with clinicopathologic parameters in NPC patients. We observed the coexpression of MMP-1 and PAR-1 in NPC tissues to be associated with advanced T-stage, advanced clinical stage, positive recurrence and metastatic status, and poor prognosis. These findings suggest that the coexpression of MMP-1 and PAR-1 may be a novel, independent marker for progression and prognosis in NPC patients. To the best of our knowledge, this is the first research on the role of the combined expression of MMP-1 and PAR-1 in a large cohort of NPC patients.

Cellular migration is a complex process that involves the breakdown of ECM, detachment of cells from the basal membrane, migration of cells from the original location, survival of cells during the migration process, invasation into the target tissue, and finally, interaction of the migrated cells with the target microenvironment. 30 Cellular migration is a critical aspect of tumor progression. The degradation of the ECM during the tumor migration and invasion processes requires the action of proteolytic enzymes, such as MMPs, which are critical for remodeling the ECM, thereby affecting cell behavior under physiologic and pathophysiologic circumstances, such as embryogenesis and tumor progression. 31 Among the 24 MMP members, the type I collagenase activity of MMP-1 has long been associated with tumor growth, invasion, and metastasis by its dual functions of both modifying the matrix and promoting vessel formation. In addition, recent studies have indicated that MMP-1 may proteolytically activate PAR-1, suggesting that MMP-1 may play a greater role in tumor progression by activating signal transduction pathways and modulating cell behavior. 32 PAR-1, as the thrombin receptor, becomes activated when thrombin cleaves a specific residue sequence (R41–S42) within the receptor’s N-terminal extracellular domain. 33 PAR-1 expression has been similarly demonstrated to correlate with tumor progression both in vitro and in vivo. In light of the potential significance of MMP-1 and PAR-1 in the tumorigenesis and tumor progression of various cancers, accumulating studies 22–24 have been performed to investigate the role of the MMP-1/PAR-1 axis in cancers. For example, the blockage of the MMP-1/PAR-1 interaction by a monoclonal antibody against PAR-1 has been shown to significantly reduce the migration ability of human mesenchymal stem cells. 35 Here, the information for tumor cell invasiveness flows from the stroma, which produces the PAR-1 activator MMP-1, to the tumor cells, which express PAR-1. This result suggests that the level of MMP-1 expression and the specific

Table 4 Multivariate Cox regression analysis of different prognostic variables in 266 nasopharyngeal carcinoma patients

<table>
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<tbody>
<tr>
<td>Clinical stage</td>
<td>I–II vs III–IV</td>
<td>6.193</td>
<td>1.011–13.392</td>
<td>0.006</td>
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<tr>
<td>Recurrence</td>
<td>No vs yes</td>
<td>6.928</td>
<td>0.922–13.556</td>
<td>0.005</td>
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<tr>
<td>Metastasis</td>
<td>No vs yes</td>
<td>6.893</td>
<td>1.023–13.528</td>
<td>0.005</td>
</tr>
<tr>
<td>MMP-I</td>
<td>Low vs high</td>
<td>3.269</td>
<td>0.732–7.038</td>
<td>NS</td>
</tr>
<tr>
<td>PAR-1</td>
<td>Low vs high</td>
<td>3.203</td>
<td>0.722–7.012</td>
<td>NS</td>
</tr>
<tr>
<td>MMP-I/Par-1</td>
<td>MMP-I-high/Par-1-low vs MMP-I-low/Par-1-high</td>
<td>9.167</td>
<td>1.332–23.836</td>
<td>0.001</td>
</tr>
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Note: NS refers to the difference without statistical significance.

Abbreviations: CI, confidence interval; HR, hazard ratio; MMP, matrix metalloproteinases; PAR, protease-activated receptor.
interaction of MMP-1 with PAR-1 proteins determine the differential migration ability of tumor cells.36,37

Recently, Agarwal et al 18 showed a strong correlation between pro-MMP-1 levels in patient fluid samples and malignancy, as well as the ability to induce migration of high PAR1-expressing OVCAR-4 cells, indicating the involvement of MMP-1/PAR-1 signaling in ovarian cancer progression. Peng et al19 reported that the MMP-1/PAR-1 signal transduction axis might be a new therapeutic target for future therapies tailored against esophageal squamous cell carcinoma. Liao et al21 found that both the overexpression of MMP-1 and PAR-1 was significantly associated with poor prognosis in hepatocellular carcinoma. Zhang et al22 demonstrated that the upregulation of MMP-1 and PAR-1 may be correlated with the histological malignancy grade and clinical outcome of glioma patients. Based on these observations, we hypothesized that the MMP-1/PAR-1 axis may play a role in NPC. According to our data in this study, MMP-1 and PAR-1 were both overexpressed in NPC tissues, which is consistent with the previous studies of Ben Nasr et al19 and Zhu et al20. Interestingly, the expression levels of MMP-1 in the NPC specimens were significantly correlated with those of PAR-1, suggesting a regulatory relationship between MMP-1 and PAR-1. In addition, we found that MMP-1 and/or PAR-1 expression levels were all associated with aggressive tumor progression and poor overall survival of the NPC patients, which is also similar with the previous findings in other cancers.22–24 More importantly, the multivariate analyses here showed that the combined MMP-1 and PAR-1 overexpression was an independent prognostic factor for overall survival (P = 0.001) in NPC patients, but the upregulation of MMP-1 and PAR-1 alone was, in each case, not an independent prognostic factors for this disease, suggesting the importance of the interaction between MMP-1 and PAR-1 in the clinical outcome of NPC patients.

In conclusion, our data provide the convincing evidence, for the first time, that the activation of the MMP-1/PAR-1 axis may be involved in the tumorigenesis and progression of NPC. The upregulation of MMP-1 in combination with PAR-1 overexpression is an unfavorable prognostic marker for NPC, which might offer the possibility of future therapeutic targets.

Disclosure
The authors report no conflicts of interest in this work.

References


