Original Article

The Effect of Matrix Metalloproteinases and Adhesion Molecules on the Prognosis in Gastric Carcinoma

Abstract

Background: Matrix metalloproteinases (MMPs), adhesion molecules, and receptors are needed in the process of cancer growth. This study aims to investigate the role of MMP-3, MMP-10, MMP-11, intercellular adhesion molecule-1 (ICAM-1), and vascular cell adhesion molecule-1 (VCAM-1) in gastric cancer. **Materials and Methods:** Fifty-two gastric carcinoma cases who underwent gastrectomy were included in the study. The cases were inspected with regard to the presence/absence of lymph node and distant metastases. The selected paraffin blocks were immunohistochemically stained with MMP 3, MMP 10, MMP 11, ICAM (CD 54), and VCAM (CD 106). **Results:** Most of the cases (*n*: 50, 94%) with gastric cancer manifested cytoplasmic staining with MMP-11. MMP-10 expression was found in 45 of 52 (86.5%), MMP-3 staining was determined in 43 (82.6%) of gastric carcinomas. Different areas of differentiation within the tumor showed differences in MMP expression in terms of intensity and extensiveness. ICAM-1 expression was found in 47 of 52 (90.4%) cases and with VCAM-1, 46/52 (88.5%) of gastric cancers manifested positive staining. Its expression was found to be higher in the nonmetastatic group both in intestinal and diffuse types. VCAM-1 was diffusely expressed in gastric cancers. However, we did not determine a significant correlation concerning differentiation and lymph node and distant metastasis. **Conclusions:** MMP-3, MMP-10, MMP-11, ICAM-1, and VCAM-1 are expressed in gastric cancers and are thought to be involved in tumor development. Levels of expression that decrease in parallel to decreasing differentiation in areas of differentiation within tumor corroborate the idea that they are related to tumor progression. Due to its relationship with metastasis, ICAM-1 expression in noncohesive cells supports the idea that ICAM-1 is a significant factor involved in metastasis development in gastric cancers. Decreased MMP-10 and MMP-11 expression in metastases suggest that these enzymes may also be linked to the metastatic potential of gastric cancers.

Keywords: *Adhesion molecule, gastric carcinoma, matrix metalloproteinase*

Zehra Bozdag, Hale Kirimlioglu[1]

Department of Pathology, Faculty of Medicine, Gaziantep University, Gaziantep, [1]Department of Pathology, Faculty of Medicine, Acibadem University, İstanbul, Turkey

Introduction

Cancers grow with progressing infiltration, invasion, degradation, and penetration of the surrounding tissues. The malignancy of a neoplasm is determined better based on invasiveness and metastasis characteristics than on other neoplastic characteristics.

Over the metastatic course, tumor cells interact with the extracellular matrix (ECM) at different stages. ECM invasion is an active event that can be understood at four steps. These are; detachment of tumor cells from each other, adherence of tumor cells to the matrix components, degradation of ECM, and migration of tumor cells.[1]

In the development of metastasis, tumor cells must first separate from each other, enter the vascular system, adhere to the endothelium and open it, and penetrate the basal membrane and reach connective tissue. Specific adhesion molecules and receptors are needed at each stage.[2] Adhesion molecules are involved at many stages of the cellular immune response. Cellular immunity is also involved in tumor immunity, and intercellular adhesion molecule-1 (ICAM-1) is important for T-cell-mediated cytotoxicity. ICAM-1 expression has been demonstrated in many malignant tumors.[3-7] Vascular cell adhesion molecule-1 (VCAM-1) is a cell adhesion molecule that is found in activated endothelial cells, dendritic cells, and renal proximal tubule cells. It is important in leukocyte-endothelial cell adhesion.[2]

Matrix metalloproteinases (MMPs) are defined as a large group of enzymes that possess the ability to degrade multiple

How to cite this article: Bozdag Z, Kirimlioglu H. The effect of matrix metalloproteinases and adhesion molecules on the prognosis in gastric carcinoma. Clin Cancer Investig J 2019;8:96-105.

Address for correspondence:
Dr. Zehra Bozdag, Department of Pathology, Faculty of Medicine, Gaziantep University, Sahinbey, Gaziantep, Turkey.
E-mail: zbozdagmd@gmail.com

Access this article online

Website: www.ccij-online.org

DOI: 10.4103/ccij.ccij_27_19

Quick Response Code:

components of the ECM.[8,9] MMPs are produced by most cells in the tumor stroma, including immune system cells that migrated to the environment. MMPs have a significant role in the repair and development of tissues. In this physiological process, MMP activity is regulated strictly. However, excess production of MMPs may contribute to the pathogenesis of inflammatory bowel diseases, cerebral hemorrhage, tumor invasion and metastasis, and rheumatoid arthritis.[9] The MMP family consists of a minimum of 25 members and all involve a zinc molecule in their active sites.[9,10] MMPs have the function of degrading matrix glycoproteins and proteoglycans.[11-13] MMPs are involved in the stimulation of angiogenesis, tumor development, and motility of tumor cells. They are believed to play a significant role in cancer spread and invasion.[14-19] Increased MMP activity and production were shown to be correlated with metastasis and aggressiveness of cancers of the colon, pancreas, prostate, lung, and breast.[20]

The main subgroups of MMPs based on substrate characteristics include: collagenases (MMP-1, 8, and 13), stromelysins (MMP-3, 10, 11, 12), matrisylins, gelatinases, membrane-type MMPs, and tissue inhibitor of metalloproteinases.[9]

Gastric carcinoma constitutes a common disease that is encountered at a varying prevalence across the world. While it is quite prevalent in Japan, Colombia, Costa Rica, and Hungary, a significant decrease has been observed in its prevalence and associated mortality in many countries.[21]

This study aims to retrospectively treat gastric carcinomas with the ICAM-1 and VCAM-1 adhesion molecules, and the MMP-3, MMP-10, MMP-11 MMPs using immunohistochemistry and investigate the roles of these agents in metastasis, which is the most important prognostic parameter of gastric carcinoma.

Materials and Methods

Fifty-two gastric carcinoma cases who underwent gastrectomy at the General Surgery Department at Inonu University Medical Faculty and received diagnoses at the Medical Pathology Department were included in the study.

The cases were inspected with regard to the presence/absence of lymph node and distant metastases. Blocks involving tumor and nontumoral areas obtained from the patients were selected. The selected blocks were immunohistochemically stained with MMP-3, MMP-10, MMP-11, ICAM-1 (CD 54), and VCAM-1 (CD 106).

Cytoplasmic staining was taken into consideration for MMPs, and apical border, cytoplasmic, membranous staining for CD54 and CD106.

Staining intensity and the extensiveness were considered in the evaluation of MMPs, CD54s, and CD106. Accordingly, staining intensity was scored from +1 to +3, respectively, as weak, moderate, and strong, whereas extensiveness was graded between 0 and 3 as follows:

- Grade 0: Staining in <25% of the cells
- Grade 1: Staining in 25%–50% of the cells
- Grade 2: Staining in 50%–75% of the cells
- Grade 3: Staining in more than 75% of the cells.

Staining characteristics in nontumoral regions were also recorded.

The dominant differentiation of the tumor in intestinal-type gastric cancers, and staining intensity and extensiveness in various areas of differentiation within the tumor were determined individually.

The presence and degree of staining in intratumoral angiolymphatic thrombi and areas of perineural infiltration were noted.

In addition, as internal controls, staining in basal glands in normal gastric mucosa and in areas of intestinal metaplasia were used as a basis.

Statistical assessments were performed using the Chi-square analysis and Fisher's exact Chi-square analysis.

Results

Of the gastric cancers included in the study, 12 were diffuse type and 40 were intestinal type. The evaluation of intestinal type gastric carcinomas with regard to their primary grades showed that 4 (10%) were well differentiated, 27 (67.5%) were moderately differentiated, and 9 (22.5%) were poorly differentiated.

Of the 19 cases who did not manifest metastasis, 4 were well, 11 were moderately, 1 poorly differentiated, 3 were signet-ring cell carcinoma; of the 14 cases who manifested lymph node metastasis, 7 were moderately, 3 were poorly differentiated, 4 were signet-ring cell carcinomas; and of the 19 cases with distant metastases, 8 were moderately differentiated. 6 were poorly differentiated, and 5 were signet-ring cell carcinomas.

MMP-11 resulted in no staining in mucous glands in the nontumoral gastric epithelium. Staining was found in crypts in the basal and in parietal cells in the corpus. Regions of intestinal metaplasia showed strong and diffuse staining. MMP-11 expression was present in both tumor cells and in connective tissue, smooth muscles, and peripheral nerve tissue.

50/52 (94%) of cases with gastric cancer manifested cytoplasmic staining with MMP-11. Both of the two cases with tumors who did not show expression had diffuse type gastric carcinomas. Of diffuse type gastric carcinomas, 4/12 presented a staining grade of +3, 2/12 of +2, and 4/12 of +1. When evaluated with regard to the extensiveness of staining, 1/12 of diffuse type of carcinomas manifested >75% MMP-11 expression, 3/12 50%–75% MMP-11 expression, 2/12 25%–50% MMP-11 expression, and 4/12 <25% MMP-11 expression [Figure 1].

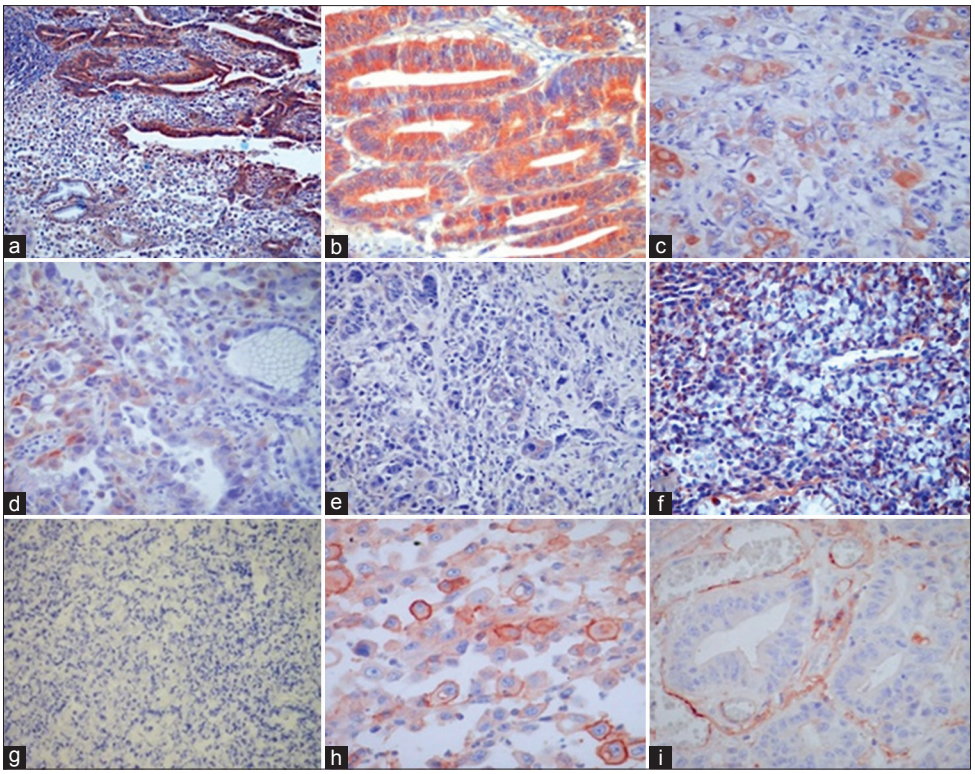

Figure 1: Matrix metalloproteinases-3, matrix metalloproteinases-10, matrix metalloproteinases-11, intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 expressions in gastric carcinomas. (a) Tumoral area shows different staining patters according to the tumor differentiation, matrix metalloproteinases-10, ×100. (b) Strong and 3+ (75%–100%) staining in well-differentiated intestinal type gastric carcinoma, matrix metalloproteinases-10, ×200. (c) Moderate and 2+ (50%–75%) staining in poorly differentiated intestinal type gastric carcinoma, matrix metalloproteinases-10, ×200. (d) Moderate and 2+ (50%–75%) staining in poorly differentiated intestinal type gastric carcinoma, matrix metalloproteinases-11, ×200. (e) Weak and 1+ (25%–50%) staining in poorly differentiated intestinal type gastric carcinoma, matrix metalloproteinases-3, ×100. (f) Moderate and 3+ (75%–100%) staining in difuse type gastric carcinoma, matrix metalloproteinases-11, ×100. (g) No staining in diffuse type gastric carcinoma, matrix metalloproteinases-3, ×100. (h) Strong membranous staining with intercellular adhesion molecule-1 in noncohesive poorly differentiated carcinoma, intercellular adhesion molecule 1, ×400. (i) Strong positive staining in endothelial cells, whereas no staining in well-differentiated carcinoma, vascular cell adhesion molecule -1, ×400

The distribution of MMP-11 expression based on the dominant differentiation of the tumor, degree and diffuseness of staining in various differentiated areas, and states of metastasis has been presented in Figure 2a for intestinal type tumors, and in Figure 2b for diffuse type carcinomas.

A cytoplasmic staining pattern was present in the case of MMP-10. MMP-10 identified MMP-10 expression in basal glands, corpus mucosa, parietal cells, while there was no staining in mucous glands. Areas of intestinal metaplasia showed diffuse staining of moderate intensity.

MMP-10 expression was found in 45/52 (86.5%) of cases with gastric cancer. The seven cases who did not show staining had diffuse type carcinomas. Diffuse type carcinomas did not manifest strong staining, and 2/12 manifested +1 and 2/12 manifested +2 MMP-10 expression. When assessed based on diffuseness of staining, 2/12 showed 25%–50%, 2/12 showed <25% MMP-10 expression [Figure 1].

The distribution of MMP-10 expressions of gastric cancers based on dominant differentiation, degree and diffuseness of staining in various differentiated areas, and metastasis states of diffuse type and intestinal type tumors is presented in Figure 3a and b.

Angiolymphatic tumor thrombi and areas of perineural infiltration showed similar characteristics with MMP-10 as well.

With MMP-3, cytoplasmic staining was present while gastric mucous glands showed no staining, and staining was found in the epithelium of the corpus mucosa, particularly in parietal cells. Areas of intestinal metaplasia showed higher MMP-3 expression.

MMP-3 staining was determined in 43/52 (82.6%) of gastric carcinomas. Of the nine cases who did not show MMP-3 expression, seven were diffuse type and two were intestinal type carcinomas. 5/12 of diffuse type carcinomas showed +1 staining. Four of these cases manifested MMP-3 expression in 25%–50% of tumor areas and two cases in <25% of tumor areas [Figure 1].

The distribution of MMP-3 expressions of gastric cancers based on the dominant differentiation of the tumor, degree, and diffuseness of staining in various differentiated areas, and their metastasis states is presented in Figure 4a and b.

Tumor cells in angiolymphatic tumor thrombi and areas of perineural infiltration were found to express MMP-11, MMP-10, and MMP-3.

No staining was found with MMP-3, MMP-10, and MMP-11 in areas of extracellular mucin. Intracellular mucin in the epithelial cells of these cases was also MMP-3 negative.

Immune staining of nontumoral gastric tissue with ICAM-1 and VCAM-1 revealed similar characteristics to staining with MMPs. The staining pattern found in gastric cancer was primarily membranous. In glands, surfaces of epithelium facing the lumen showed apical staining.

Germinal centers showed strong staining with ICAM-1 and vessel endothelia showed strong staining with VCAM-1 [Figure 1].

47/52 (90.4%) cases stained positive with ICAM-1. Of the five cases who manifested no staining, two were intestinal type and three were diffuse type carcinomas. All intestinal type carcinomas were poorly differentiated carcinomas. The three diffuse type cases who did not present ICAM-1 expression belonged to the distant metastasis group. Staining was +3 in 1/12, +2 in 5/12, and +1 in 3/12 of diffuse type gastric carcinomas. When evaluated based on the extensiveness of staining, 2/12 showed more than 75%, 1/12 50%–75%, 2/12 25%–50%, and 4/12 < 25% ICAM-1 expression.

Poorly differentiated noncohesive cells demonstrated membranous ICAM-1 staining of +3 intensity.

Cases that formed well-differentiated glandular structures showed strong membranous ICAM-1 staining patterns in cells that shed off into the lumen. In these regions, cells that formed glands showed apical staining.

The distribution of ICAM-1 expression manifested by gastric cancers based on the dominant differentiation of the tumor, degree, and diffuseness of staining in various differentiated areas, and their states of metastasis is presented in Figure 5a and b.

With VCAM-1, 46/52 (88.5%) of gastric cancers manifested positive staining. Of the six cases who did not show staining, three were intestinal type and three were diffuse type carcinomas.

Among diffuse type gastric carcinomas, staining grades of +3 were determined in 1/12, +2 in 6/12, and +1 in 2/12. When evaluated based on the diffuseness of staining, 8/12 showed 50%–75%, 3/12 25%–50%, and 1/12 <25% VCAM-1 expression [Figure 1].

The distribution of VCAM-1 expression manifested by gastric cancers based on the dominant differentiation of the tumor, degree, and diffuseness of staining in various differentiated areas, and their states of metastasis is presented in Figure 6a and b.

Angiolymphatic tumor thrombi demonstrated expression with ICAM-1, VCAM-1, and MMP-3-10-11. MMPs produced more pronounced staining in areas of perineural invasion.

Of the 40 intestinal type carcinoma cases, 16 did not have metastasis, 10 had only lymph node metastasis, and 14 had distant metastasis. Whereas of the 12 diffuse type cases, three did not have metastasis, four had lymph node metastasis, and five had distant metastasis.

The intensity of MMP and adhesion molecule expressions in gastric cancers was investigated with regard to their relationship with metastasis.

With MMP-11, 4/16 of nonmetastatic intestinal type carcinoma cases showed +3 staining, 7/16 +2 staining, 5/16 +1 staining; of cases with lymph node metastases, 4/10 showed +3, 2/10 showed +2, and 4/10 showed +1 staining; and of cases with distant metastases, 2/14 showed +3 staining, 5/14 +2 staining, 5/14 +1 staining, while 2/14 did not show MMP-11 expression. Among cases of diffuse type carcinoma, 1/3 of nonmetastatic cases showed +3 staining, while 2/3 were negative; of cases with lymph node metastasis, 3/4 showed +2 and 1/4 showed +1 staining; and of cases with metastasis, 2/5 showed +3, and 3/5 +1 staining.

With MMP-10, 11/16 of nonmetastatic intestinal type carcinoma cases showed +3 staining, 4/16 +2 staining, 1/16 +1 staining; of cases with lymph node metastasis, 3/10 showed +3, 5/10 showed +2, and 2/10 showed +1 staining; and of cases with distant metastasis, 2/14 showed +3 staining, 8/14 +2 staining, and 4/14 +1 staining. Among cases of diffuse type carcinoma, 2/3 of nonmetastatic cases showed +2 staining, while 1/3 were negative; of cases with lymph node metastasis, 1/4 showed +2 staining while 3/4 did not show MMP-10 expression. Of cases with metastasis, 3/5 showed +1, and 2/5 were MMP-10-negative.

With MMP-3, 8/16 of nonmetastatic intestinal type carcinoma cases showed +3 staining, 7/16 +2 staining, 1/16 +1 staining; of cases with lymph node metastasis, 1/10 showed +3, 2/10 showed +2, 5/10 showed +1 staining, while 2/10 were MMP-3-negative; and of cases with distant metastasis, 7/14 showed +3 staining, 5/14 +2 staining, 1/14 +1 staining, while 1/14 showed no MMP-3 expression. Among cases of diffuse type carcinoma, 1/3 of nonmetastatic cases showed +1 staining, while 2/3 were negative; of cases with lymph node metastasis 2/4 showed +1 staining while 2/4 did not show MMP-3 expression; of cases with metastasis, 2/5 showed +1, and 3/5 were MMP-3-negative.

With VCAM-1, 4/16 of nonmetastatic intestinal type carcinoma cases showed +3 staining, 7/16 +2 staining, 5/16 +1 staining; of cases with lymph node metastasis, 4/10 showed +3, 2/10 showed +2, and 4/10 showed +1 staining; and of cases with distant metastasis, 2/14 showed +3 staining, 5/14 +2 staining, 5/14 +1 staining, while 2/14 showed no VCAM-1 expression. Among cases of diffuse type carcinoma, 2/3 of nonmetastatic cases showed +2 staining, while 1/3

were negative; of cases with lymph node metastasis 1/4 showed +3 staining, 2/4 +2 staining, while 1/4 did not show MMP-3 expression; of cases with metastasis, 2/5 showed +2 staining, 2/5 +1 staining, and 1/5 were MMP-3-negative.

With ICAM-1, 5/16 of nonmetastatic intestinal type carcinoma cases showed +3 staining, 9/16 +2 staining, 2/16 +1 staining; of cases with lymph node metastasis, 6/10 showed +3, 2/10 showed +2, and 1/10 showed +1 staining; and of cases with distant metastasis, 2/14 showed +3 staining, 8/14 +2 staining, while 4/14 showed no ICAM-1 expression. Among cases of diffuse type carcinoma, 1/3 of nonmetastatic cases showed +3 staining and 2/3 +1 staining; of cases with lymph node metastasis 3/4 showed +2 staining and 1/4 showed +1 staining; and of cases with metastasis, 2/5 showed +2 staining, and 3/5 were MMP-3-negative.

The relationship between percentages of MMP-3, MMP-10, MMP-11, ICAM, and VCAM staining intensities and metastasis is demonstrated in Figures 2-6.

Discussion

Tumor development and metastasis formation are consequences of cell-cell and cell-ECM relationships managed by cell adhesion molecules. In the development of metastases, tumor cells must complete all of the stages that include transformation, growth, angiogenesis, invasion, survival in circulation, adhesion, extravasation, proliferation, and further angiogenesis at the metastasis site.[1,22] In this process, the tumor must divide at its focus, enter the vascular system, adhere to the endothelium and open it, and penetrate the basement membrane and reach connective tissue. At each stage, specific adhesion molecules and receptors are required.[2]

Adhesion molecules are involved in various stages of the cellular immune response. Among adhesion molecules, ICAM-1 plays a role at the first stage of adhesion of T-cells onto the target cells.[3] Cellular immunity plays a major role in tumor immunity, and ICAM-1 is important in T-cell-mediated cytotoxicity.[3,23] ICAM-1 expression was shown to be present in multiple malignant tumors including those of the bladder, colon, thyroid, renal carcinomas, melanomas, and lymphoid malignancies.[3-7]

In a study by Nasu *et al*.[23] the ICAM-1-produced staining in approximately half of the gastric cancers, and no ICAM-1 expression was detected in the normal gastric epithelium. ICAM-1 expression is present on the luminal surface in intestinal type carcinomas, whereas it is rare in diffuse type carcinomas. ICAM-1 expression is higher in intestinal type carcinoma cells than in diffuse type carcinoma cells with statistical significance. However, the study in the literature did not investigate the relationship that differentiation grades of gastric carcinomas had with ICAM-1 expression and the tumor developing lymph node or distant metastases.

A study conducted with flow cytometric analysis similarly found that ICAM-1 was absent in the normal gastric epithelium and that its levels in carcinoma cells that metastasized to the peritoneum were significantly higher than in carcinoma cells.[6] On the other hand, decreased levels of ICAM-1 expression in cancerous cells were determined to be related to the development of lymph node metastasis in a study conducted by Tanaka *et al*.[24] Again, serum ICAM-1 levels were determined to be correlated with advanced stages, metastatic cases, and an unfavorable prognosis.[25] Our study found that the relationship between strong membranous ICAM-1 positivity and distant metastasis was significant.

Vascular cell adhesion molecule (VCAM-1) is a cell adhesion molecule that is found in activated endothelial cells, dendritic cells, and renal proximal tubule cells. It is important for leukocyte-endothelial cell adhesion.[2]

VCAM-1 was demonstrated in gastric malignant tumors using immunohistochemistry, and it was reported to play a stimulating role in angiogenesis.[26] In a study by Ding *et al*.,[27] VCAM-1 was assessed in serum and gastric cancers using immunohistochemistry. It was found that serum levels of VCAM-1 were significantly higher in patients with gastric cancer, with immunopositivity in 75.6% of the cases. Furthermore, the mentioned study found that VCAM-1-positive gastric cancers were more invasive and were of more advanced stages. It was found to be related to lymph node metastasis

A study conducted by Velikova *et al*. found that serum levels of ICAM-1 and VCAM-1 were significantly higher and that high VCAM-1 levels were connected to decreased survival time.[2]

Diverging from studies in the literature, our study determined no significant relationship between VCAM-1 and metastasis development.

Besides adhesion molecules, certain proteolytic enzymes, particularly MMPs, play a significant role in degrading the basement membranes of the epithelium and endothelium and the ECM during the migration and infiltration of cancer cells.[10,28] To this day, more than 25 MMPs have been identified. They can be classified under four subgroups as follows: collagenases, gelatinases, stromelysins, and membrane-type MMPs.[1,9]

Many experimental and clinicopathological studies have shown a relationship between MMP expression and invasive phenotype in tumor cells.[10,29] Numerous studies have been conducted on MMP expression and production in gastric cancers, particularly in Japan.[30-32]

MMP-3 (stromelysin-1), MMP-10 (stromelysin-2), and MMP-11, which were included in our study, belong to the same group. MMPs of this group do not degrade themselves but catalyze the degradation process. Their roles in carcinogenesis, metastasis, and prognosis in gastric

cancers have not been determined. We showed in this study that this group of MMPs was expressed strongly in gastric cancers, especially in the intestinal type. Their more intense and diffuse expression in areas of intestinal metaplasia and dysplasia suggests that they are involved in tumor development. Their expression decreases in parallel to a decrease in differentiation within the tumor.

An immunohistochemical literature study conducted with MMP-3 reported no staining in normal gastric mucosa, and MMP-3 expression in 27% of tumors.[28] However, a study conducted using *in situ* hybridization detected no MMP-3 expression in gastric cancers.[31] In our study, while there was no staining with MMP-3 in the antral mucosa, staining was detected in parietal cells in the corpus, as seen with other MMPs. The study conducted earlier includes no information about whether or not evaluations were performed with regard to sections of the stomach. In this study, MMP-3 expression in gastric cancers was found to be higher than reported in the other immunohistochemical study in the literature. Studies in the literature that compared MMP-3 expression and lymph node metastasis with survival time found no significant relationships.[28,33] Similarly, our study did not find a significant relationship between the state of metastasis and MMP-3 expression either, but a relative loss in MMP-3 expression was observed in tumors with distant metastasis.

The literature has shown MMP-10 expression in tumors with an epithelial origin such as lung, head-neck, esophagus and oral squamous cell carcinomas, basal, and squamous cell carcinomas of the skin.[34-37] Differently from many other MMPs that are mainly localized in the tumor stroma, MMP-10 is expressed by the tumor cells.[36,38,39] This expression profile and the wide substrate specificity of MMP-10 corroborate the notion that it could be a target in treatment attempts.[36,37,40-42] In our study, MMP-10 expression was found to be higher in cases without metastasis, both in intestinal and diffuse types.

An increase in MMP-11 expression in tumors was first shown in invasive breast carcinomas and has later been reported in relation to various cancers including lung and colorectal cancers.[43-45] The increase in MMP-11 expression is thought to be an early stage change that could have an aggravating effect on tumor progression.[46,47] MMP-11 is correlated with an unfavorable prognosis in head-neck cancers.[48] It is an independent prognostic

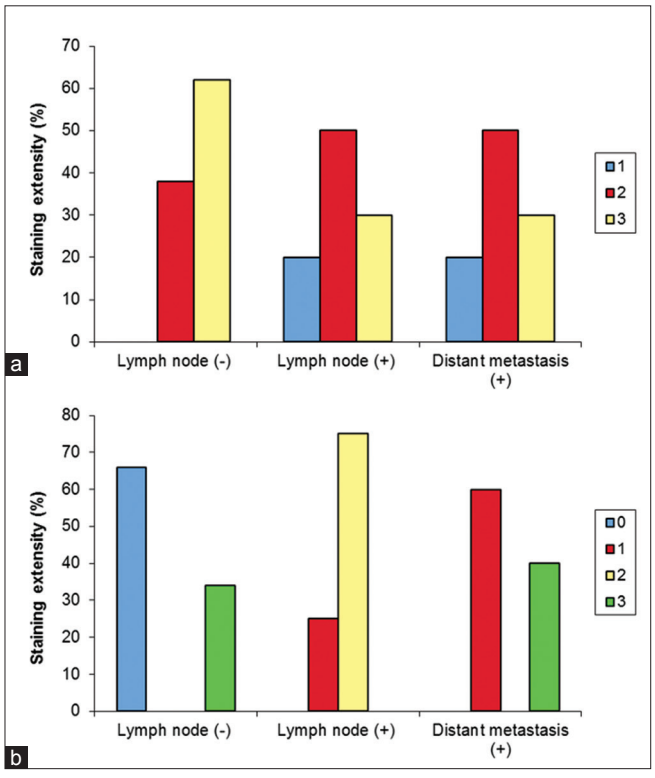

Figure 2: The distribution of matrix metalloproteinases-11, matrix metalloproteinases-10, matrix metalloproteinases-3, intercellular adhesion molecule and vascular cell adhesion molecule expressions based on the dominant differentiation of the tumor, degree and extensity of staining in various differentiated areas, and states of metastasis for intestinal type and diffuse type carcinomas. (a) Matrix metalloproteinases-11 expression in intestinal type carcinoma and its relationship with metastasis. (b) Matrix metalloproteinases-11 expression in diffuse carcinoma and its relationship with metastasis

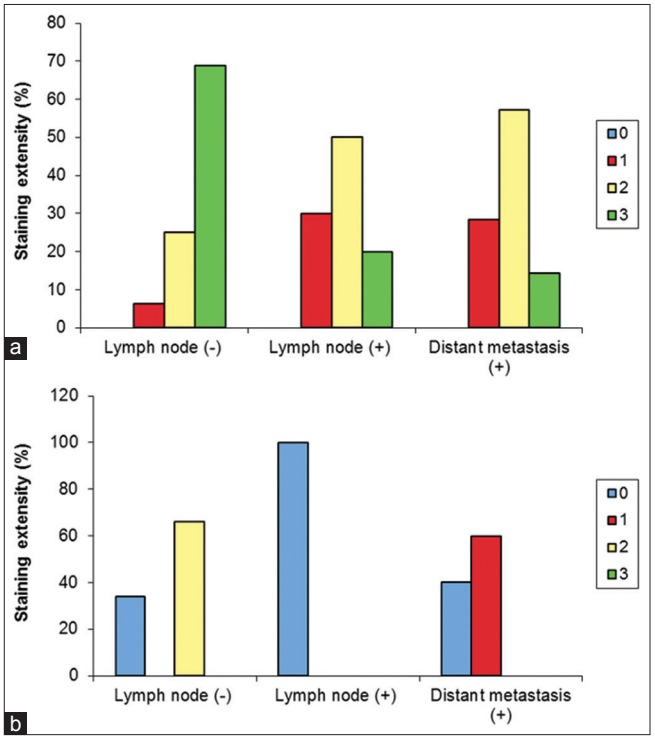

Figure 3: The distribution of matrix metalloproteinases-11, matrix metalloproteinases-10, matrix metalloproteinases-3, intercellular adhesion molecule and vascular cell adhesion molecule expressions based on the dominant differentiation of the tumor, degree and extensity of staining in various differentiated areas, and states of metastasis for intestinal type and diffuse type carcinomas. (a) Matrix metalloproteinases-10 expression in intestinal type carcinoma and its relationship with metastasis. (b) Matrix metalloproteinases-11 expression in diffuse carcinoma and its relationship with metastasis

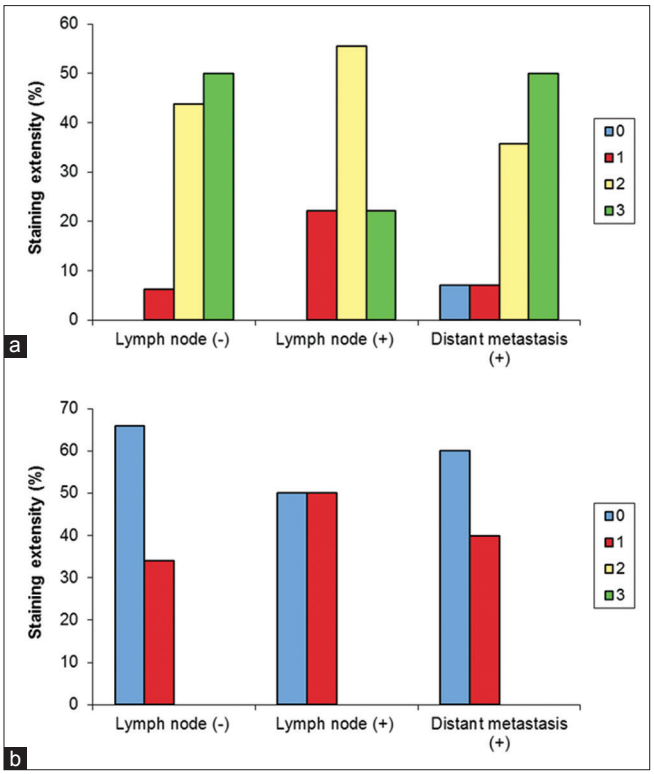

Figure 4: The distribution of matrix metalloproteinases-11, matrix metalloproteinases-10, matrix metalloproteinases-3, intercellular adhesion molecule and vascular cell adhesion molecule expressions based on the dominant differentiation of the tumor, degree and extensity of staining in various differentiated areas, and states of metastasis for intestinal type and diffuse type carcinomas. (a) Matrix metalloproteinases-3 expression in intestinal type carcinoma and its relationship with metastasis. (b) Matrix metalloproteinases-3 expression in diffuse carcinoma and its relationship with metastasis

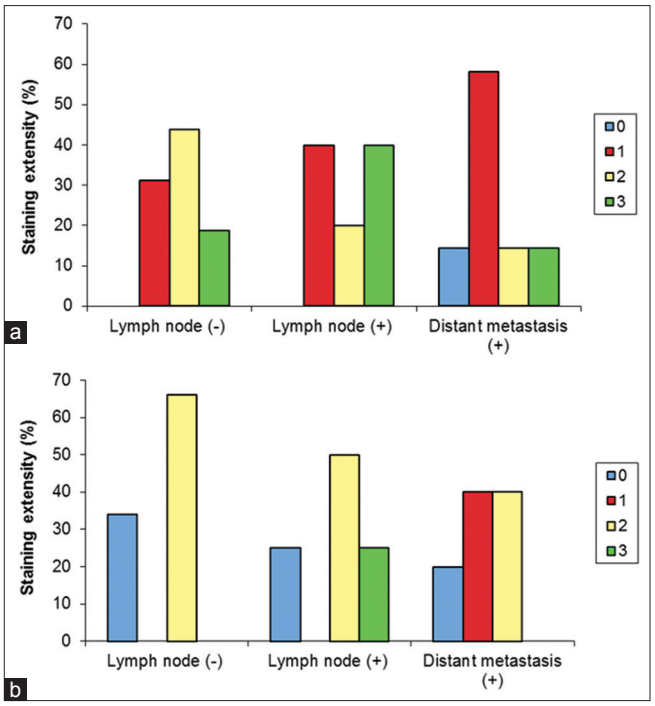

Figure 5: The distribution of matrix metalloproteinases-11, matrix metalloproteinases-10, matrix metalloproteinases-3, intercellular adhesion molecule and vascular cell adhesion molecule expressions based on the dominant differentiation of the tumor, degree and extensity of staining in various differentiated areas, and states of metastasis for intestinal type and diffuse type carcinomas. (a) Vascular cell adhesion molecule expression in intestinal type carcinoma and its relationship with metastasis. (b) Vascular cell adhesion molecule expression in diffuse carcinoma and its relationship with metastasis

marker for disease-free survival time in breast cancers.[49] In invasive bladder carcinomas, MMP-11 is related to tumor aggressiveness[50] In lung cancers excluding small cell, increased MMP-11 expression is connected to lymph node metastasis.[51] High MMP-11 levels are related to an unfavorable prognosis in astrocytic tumors and squamous cell tumors of the esophagus.[52-54] In a study done on gastric cancers that evaluated MMP-11 expression using polymerized chain reaction, MMP-11 expression was determined to be higher in gastric carcinomas.[55] The authors of this study suggested that a decrease in MMP-11 inhibited cell proliferation and tumor development in gastric carcinomas and MMP-11 could constitute a therapeutic target in gastric carcinomas. In our study, MMP-11 expression was determined to be higher in cases without metastasis in intestinal type carcinomas and in cases with distant metastasis in diffuse type carcinomas.

Conclusions

In this retrospective study, we conducted on our cases with gastric cancer, MMP-3, MMP-10, MMP-11 among MMPs, and ICAM-1 and VCAM-1 among cell adhesion molecules were determined to be expressed in gastric cancers. This expression was diffuse across all MMPs, although less in MMP-3. MMP-3, MMP-10, and MMP-11 expressions were of similar pattern, intensity, and extensiveness.

Different areas of differentiation within the tumor showed differences in MMP expression in terms of intensity and extensiveness. In intestinal type tumors, the expression of all three MMPs of the stromelysin group decreased in parallel to a decrease in differentiation within the tumor.

However, when evaluated with regard to dominant differentiations, no significant relationship was found between differentiation and MMP expression in intestinal type carcinomas.

MMP expressions in the diffuse type were lower than in the intestinal type and most cases which did not demonstrate MMP expression were of the diffuse type.

With ICAM-1, strong, diffusive expression was determined in gastric cancers, especially in noncohesive cells. Cases with distant metastases showed membranous-pattern positivity detected in poorly differentiated areas.

ICAM-1 also produced strong, diffusive positivity in angiolymphatic tumor thrombi. Its expression was found to be higher in the nonmetastatic group than the metastatic group, both in intestinal and diffuse types.

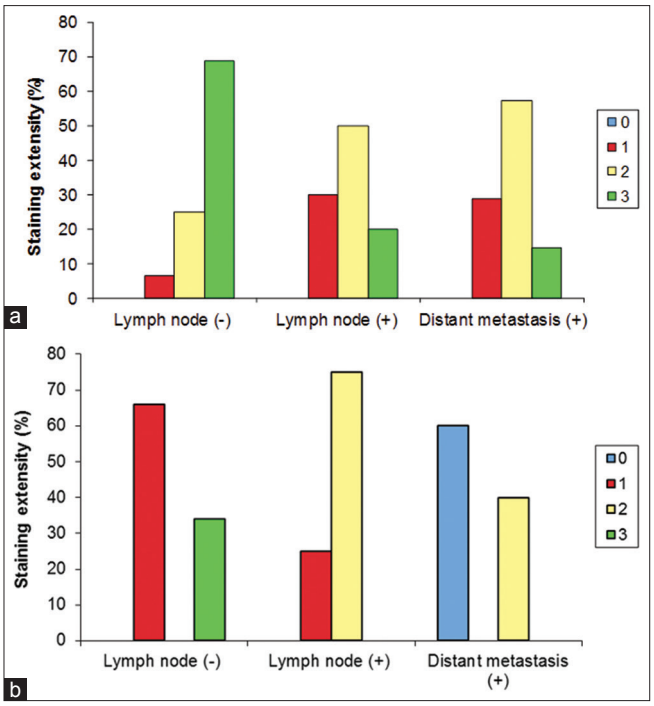

Figure 6: The distribution of matrix metalloproteinases-11, matrix metalloproteinases-10, matrix metalloproteinases-3, intercellular adhesion molecule and vascular cell adhesion molecule expressions based on the dominant differentiation of the tumor, degree and extensity of staining in various differentiated areas, and states of metastasis for intestinal type and diffuse type carcinomas. (a) Intercellular adhesion molecule expression in intestinal type carcinoma and its relationship with metastasis. (b) Intercellular adhesion molecule expression in diffuse carcinoma and its relationship with metastasis

VCAM-1 was diffusely expressed in gastric cancers. However, we did not determine a significant correlation concerning differentiation and lymph node and distant metastasis as opposed to reports in the literature.

When evaluated with regard to distant metastases, MMP-10 expression was stronger in the nonmetastatic group than in the metastatic group both in intestinal and diffuse types; MMP-11 expression was stronger in the nonmetastatic group than in the metastatic group in the intestinal type and weaker in the diffuse type. With MMP-3, no significant difference was determined in terms of metastasis.

In conclusion, MMP-3, MMP-10, MMP-11, ICAM-1, and VCAM-1 are expressed in gastric cancers and are thought to be involved in tumor development.

Levels of expression that decrease in parallel to decreasing differentiation in areas of differentiation within tumor corroborate the idea that they are related to tumor progression.

Due to its relationship with metastasis, ICAM-1 expression in noncohesive cells supports the idea that ICAM-1 is a significant factor involved in metastasis development in gastric cancers in accordance with the literature data.

Decreased MMP-10 and MMP-11 expression in metastases suggest that these enzymes may also be linked to the metastatic potential of gastric cancers.

Acknowledgments

This study was supported by scientific research projects governing unit (BAPYB) of Inonu University.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Kumar V, Abbas AK, Aster JC. Robbins Basic Pathology. 9th ed.. Philadelphia, PA: Elsevier; 2008. p. 68, 192-4.
2. Velikova G, Banks RE, Gearing A, Hemingway I, Forbes MA, Preston SR, *et al.* Circulating soluble adhesion molecules E-cadherin, E-selectin, intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) in patients with gastric cancer. Br J Cancer 1997;76:1398-404.
3. Campbell SC, Tanabe K, Alexander JP, Edinger M, Tubbs RR, Klein EA. Intercellular adhesion molecule-1 expression by bladder cancer cells: Functional effects. J Urol 1994;151:1385-90.
4. Horst E, Radaszkiewicz T, Hooftman-den Otter A, Pieters R, van Dongen JJ, Meijer CJ, *et al.* Expression of the leucocyte integrin LFA-1 (CD11a/CD18) and its ligand ICAM-1 (CD54) in lymphoid malignancies is related to lineage derivation and stage of differentiation but not to tumor grade. Leukemia 1991;5:848-53.
5. Koyama S, Ebihara T, Fukao K. Expression of intercellular adhesion molecule 1 (ICAM-1) during the development of invasion and/or metastasis of gastric carcinoma. J Cancer Res Clin Oncol 1992;118:609-14.
6. Natali P, Nicotra MR, Cavaliere R, Bigotti A, Romano G, Temponi M, *et al.* Differential expression of intercellular adhesion molecule 1 in primary and metastatic melanoma lesions. Cancer Res 1990;50:1271-8.
7. Tomita Y, Nishiyama T, Watanabe H, Fujiwara M, Sato S. Expression of intercellular adhesion molecule-1 (ICAM-1) on renal-cell cancer: Possible significance in host immune responses. Int J Cancer 1990;46:1001-6.
8. Liu JR, Yang BF, Chen BQ, Yang YM, Dong HW, Song YQ. Inhibition of beta-ionone on SGC-7901 cell proliferation and upregulation of metalloproteinases-1 and -2 expression. World J Gastroenterol 2004;10:167-71.
9. Mirastschijski U, Dinesh N, Baskaran S, Wedekind D, Gavrilovic J, Murray MY, *et al.* Novel specific human and mouse stromelysin-1 (MMP-3) and stromelysin-2 (MMP-10) antibodies for biochemical and immunohistochemical analyses. Wound Repair Regen 2019. [Epub ahead of print].
10. Nomura H, Fujimoto N, Seiki M, Mai M, Okada Y. Enhanced production of matrix metalloproteinases and activation of matrix metalloproteinase 2 (gelatinase A) in human gastric carcinomas. Int J Cancer 1996;69:9-16.
11. Heslin MJ, Yan J, Johnson MR, Weiss H, Diasio RB, Urist MM. Role of matrix metalloproteinases in colorectal carcinogenesis. Ann Surg 2001;233:786-92.
12. Honda M, Mori M, Ueo H, Sugimachi K, Akiyoshi T. Matrix metalloproteinase-7 expression in gastric carcinoma. Gut 1996;39:444-8.
13. Franchi A, Santucci M, Masini E, Sardi I, Paglierani M, Gallo O. Expression of matrix metalloproteinase 1, matrix metalloproteinase 2, and matrix metalloproteinase 9 in carcinoma

of the head and neck. Cancer 2002;95:1902-10.
14. Kumar A, Collins H, Van Tam J, Scholefield JH, Watson SA. Effect of preoperative radiotherapy on matrilysin gene expression in rectal cancer. Eur J Cancer 2002;38:505-10.
15. Łukaszewicz-Zając M, Gryko M, Pączek S, Szmitkowski M, Kędra B, Mroczko B, *et al.* Matrix metalloproteinase 2 (MMP-2) and its tissue inhibitor 2 (TIMP-2) in pancreatic cancer (PC). Oncotarget 2019;10:395-403.
16. Liu X, Su C, Xu J, Zhou D, Yan H, Li W. Immunohistochemical analysis of matrix metalloproteinase-9 predicts papillary thyroid carcinoma prognosis. Oncol Lett 2019;17:2308-16.
17. Guo H, Sun Z, Wei J, Xiang Y, Qiu L, Guo L. Expressions of matrix metalloproteinases-9 and tissue inhibitor of metalloproteinase-1 in pituitary adenomas and their relationships with prognosis. Cancer Biother Radiopharm 2019;34:1-6.
18. Tanaka T, Terai Y, Ohmichi M. Association of matrix metalloproteinase-9 and decorin expression with the infiltration of cervical cancer. Oncol Lett 2019;17:1306-12.
19. Pakkanen PP, Aaltonen LM, Sorsa TA, Tervahartiala TI, Hagström JK, Ilmarinen TT. Serum matrix metalloproteinase 8 and tissue inhibitor of metalloproteinase 1: Potential markers for malignant transformation of recurrent respiratory papillomatosis and for prognosis of laryngeal cancer. Head Neck 2019;41:309-14.
20. Bendardaf R, Lamlum H, Vihinen P, Ristamäki R, Laine J, Pyrhönen S. Low collagenase-1 (MMP-1) and MT1-MMP expression levels are favourable survival markers in advanced colorectal carcinoma. Oncology 2003;65:337-46.
21. Lauwers GY, Carnerio F, Graham DY, Curado MP, Franceschi S, Montgomery E, *et al*. Tumours of the stomach. In: Bosman FT, Carnerio F, Hruban RH, Theise ND, editors. WHO Classification of Tumours of the Digestive System. 4th ed. Lyon: International Agency for Research on Cancer; 2010. p. 48.
22. Takahashi Y, Kitadai Y, Ellis LM, Bucana CD, Fidler IJ, Mai M. Multiparametric *in situ* mRNA hybridization analysis of gastric biopsies predicts lymph node metastasis in patients with gastric carcinoma. Jpn J Cancer Res 2002;93:1258-65.
23. Nasu R, Mizuno M, Kiso T, Shimo K, Uesu T, Nasu J, *et al.* Immunohistochemical analysis of intercellular adhesion molecule-1 expression in human gastric adenoma and adenocarcinoma. Virchows Arch 1997;430:279-83.
24. Tanaka H, Yashiro M, Sunami T, Ohira M, Hirakawa YS. Lipid-mediated gene transfection of intercellular adhesion molecule-1 suppresses the peritoneal metastasis of gastric carcinoma. Int J Mol Med 2002;10:613-7.
25. Polychronidis AC, Tsaroucha AK, Samolis SP, Botaitis SK, Perente SS, Simopoulos CE. Serum levels of intercellular adhesion molecule-1 correlate with advanced and metastatic disease and poor prognosis in gastric cancer. Folia Med (Plovdiv) 2003;45:20-4.
26. Yu JX, Zhang XT, Liao YQ, Zhang QY, Chen H, Lin M, *et al.* Relationship between expression of CD105 and growth factors in malignant tumors of gastrointestinal tract and its significance. World J Gastroenterol 2003;9:2866-9.
27. Ding YB, Chen GY, Xia JG, Zang XW, Yang HY, Yang L. Association of VCAM-1 overexpression with oncogenesis, tumor angiogenesis and metastasis of gastric carcinoma. World J Gastroenterol 2003;9:1409-14.
28. Stetler-Stevenson WG, Aznavoorian S, Liotta LA. Tumor cell interactions with the extracellular matrix during invasion and metastasis. Annu Rev Cell Biol 1993;9:541-73.
29. Murray GI, Duncan ME, Arbuckle E, Melvin WT, Fothergill JE. Matrix metalloproteinases and their inhibitors in gastric cancer. Gut 1998;43:791-7.
30. Otani Y, Okazaki I, Arai M, Kameyama K, Wada N, Maruyama K, *et al.* Gene expression of interstitial collagenase (matrix metalloproteinase 1) in gastrointestinal tract cancers. J Gastroenterol 1994;29:391-7.
31. Okayama H, Kumamoto K, Saitou K, Hayase S, Kofunato Y, Sato Y, *et al.* CD44v6, MMP-7 and nuclear Cdx2 are significant biomarkers for prediction of lymph node metastasis in primary gastric cancer. Oncol Rep 2009;22:745-55.
32. McDonnell S, Navre M, Coffey RJ Jr., Matrisian LM. Expression and localization of the matrix metalloproteinase pump-1 (MMP-7) in human gastric and colon carcinomas. Mol Carcinog 1991;4:527-33.
33. Zhang J, Jin X, Fang S, Li Y, Wang R, Guo W, *et al.* The functional SNP in the matrix metalloproteinase-3 promoter modifies susceptibility and lymphatic metastasis in esophageal squamous cell carcinoma but not in gastric cardiac adenocarcinoma. Carcinogenesis 2004;25:2519-24.
34. Gill JH, Kirwan IG, Seargent JM, Martin SW, Tijani S, Anikin VA, *et al.* MMP-10 is overexpressed, proteolytically active, and a potential target for therapeutic intervention in human lung carcinomas. Neoplasia 2004;6:777-85.
35. Liu H, Qin YR, Bi J, Guo A, Fu L, Guan XY. Overexpression of matrix metalloproteinase 10 is associated with poor survival in patients with early stage of esophageal squamous cell carcinoma. Dis Esophagus 2012;25:656-63.
36. Kerkelä E, Ala-aho R, Lohi J, Grénman R, M-Kähäri V, Saarialho-Kere U. Differential patterns of stromelysin-2 (MMP-10) and MT1-MMP (MMP-14) expression in epithelial skin cancers. Br J Cancer 2001;84:659-69.
37. O-Charoenrat P, Rhys-Evans PH, Eccles SA. Expression of matrix metalloproteinases and their inhibitors correlates with invasion and metastasis in squamous cell carcinoma of the head and neck. Arch Otolaryngol Head Neck Surg 2001;127:813-20.
38. Foda HD, Zucker S. Matrix metalloproteinases in cancer invasion, metastasis and angiogenesis. Drug Discov Today 2001;6:478-82.
39. Muller D, Breathnach R, Engelmann A, Millon R, Bronner G, Flesch H, *et al.* Expression of collagenase-related metalloproteinase genes in human lung or head and neck tumours. Int J Cancer 1991;48:550-6.
40. Mathew R, Khanna R, Kumar R, Mathur M, Shukla NK, Ralhan R. Stromelysin-2 overexpression in human esophageal squamous cell carcinoma: Potential clinical implications. Cancer Detect Prev 2002;26:222-8.
41. Duffy MJ, Maguire TM, Hill A, McDermott E, O'Higgins N. Metalloproteinases: Role in breast carcinogenesis, invasion and metastasis. Breast Cancer Res 2000;2:252-7.
42. Vihinen P, Kähäri VM. Matrix metalloproteinases in cancer: Prognostic markers and therapeutic targets. Int J Cancer 2002;99:157-66.
43. Basset P, Bellocq JP, Wolf C, Stoll I, Hutin P, Limacher JM, *et al.* A novel metalloproteinase gene specifically expressed in stromal cells of breast carcinomas. Nature 1990;348:699-704.
44. Johnson LD, Hunt DM, Kim K, Nachtigal M. Amplification of stromelysin-3 transcripts from carcinomas of the colon. Hum Pathol 1996;27:964-8.
45. Urbanski SJ, Edwards DR, Maitland A, Leco KJ, Watson A, Kossakowska AE. Expression of metalloproteinases and their inhibitors in primary pulmonary carcinomas. Br J Cancer 1992;66:1188-94.
46. Bolon I, Brambilla E, Vandenbunder B, Robert C, Lantuejoul S, Brambilla C. Changes in the expression of matrix proteases

and of the transcription factor c-ets-1 during progression of precancerous bronchial lesions. Lab Invest 1996;75:1-13.

47. Soni S, Mathur M, Shukla NK, Deo SV, Ralhan R. Stromelysin-3 expression is an early event in human oral tumorigenesis. Int J Cancer 2003;107:309-16.
48. Muller D, Wolf C, Abecassis J, Millon R, Engelmann A, Bronner G, *et al.* Increased stromelysin 3 gene expression is associated with increased local invasiveness in head and neck squamous cell carcinomas. Cancer Res 1993;53:165-9.
49. Basset P, Wolf C, Chambon P. Expression of the stromelysin-3 gene in fibroblastic cells of invasive carcinomas of the breast and other human tissues: A review. Breast Cancer Res Treat 1993;24:185-93.
50. Mueller J, Steiner C, Höfler H. Stromelysin-3 expression in noninvasive and invasive neoplasms of the urinary bladder. Hum Pathol 2000;31:860-5.
51. Delebecq TJ, Porte H, Zerimech F, Copin MC, Gouyer V, Dacquembronne E, *et al.* Overexpression level of stromelysin 3 is related to the lymph node involvement in non-small cell lung cancer. Clin Cancer Res 2000;6:1086-92.
52. Thorns V, Walter GF, Thorns C. Expression of MMP-2, MMP-7, MMP-9, MMP-10 and MMP-11 in human astrocytic and oligodendroglial gliomas. Anticancer Res 2003;23:3937-44.
53. Porte H, Triboulet JP, Kotelevets L, Carrat F, Prévot S, Nordlinger B, *et al.* Overexpression of stromelysin-3, BM-40/SPARC, and MET genes in human esophageal carcinoma: Implications for prognosis. Clin Cancer Res 1998;4:1375-82.
54. Rio MC. From a unique cell to metastasis is a long way to go: Clues to stromelysin-3 participation. Biochimie 2005;87:299-306.
55. Deng H, Guo RF, Li WM, Zhao M, Lu YY. Matrix metalloproteinase 11 depletion inhibits cell proliferation in gastric cancer cells. Biochem Biophys Res Commun 2005;326:274-81.