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The Role of Matrix Metalloproteinase-9 (MMP-9) as a Prognostic Factor in Epithelial and Lymphatic Neoplasia

V. Pârvănescu¹, M. Georgescu¹, I. Georgescu², V. Șurlin², Ș. Pătrașcu², A.M. Picleanu³, E. Georgescu²

¹Department of Plastic Surgery, Emergency County Hospital of Craiova, Romania

²Department of Surgery, University of Medicine and Pharmacy of Craiova, Romania

³Department of Hematology, Filantropia Clinical Hospital of Craiova, Romania

Rezumat

Rolul matrix metaloproteinazei-9 (MMP-9) ca factor de prognostic în neoplasmele epiteliale și limfatice

Matrix metaloproteinaza 9 (MMP-9) este o endopeptidază zinc-dependență remodelantă a matrixului extracelular, direct implicată în mecanismele de invazie locală și în metastazare. Scopul acestui review este de a evalua expresia MMP-9 și valoarea ei prognostică în cele mai frecvente neoplasme epiteliale și limfatice ale regiunii abdomino-pelvine. Am inclus 19 studii publicate între 1 ianuarie 1995 și 31 iulie 2015, totalizând 1523 de pacienți. Analiza acestora a evidențiat faptul că MMP-9 constituie un marker valid pentru o supraviețuire redusă în neoplasmele epiteliale și limfatice.

Cuvinte cheie: MMP-9, carcinom, limfom, matrix metaloproteinaza

Abstract

Matrix metalloproteinase 9 is a zinc-dependent extracellular matrix remodeling endopeptidase directly involved in the

local invasion mechanisms and in metastasis. The current review aims to evaluate the expression of MMP-9 and its prognostic value in the most common epithelial and lymphatic neoplasia of the pelvic-abdominal region. We included 19 studies published between January 1st, 1995 and July 31st 2015, involving a total of 1523 patients. The analysis indicate that MMP-9 is valid marker of poor survival in epithelial and lymphatic neoplasia.

Key words: MMP-9, carcinoma, lymphoma, matrix metalloproteinase

Introduction

The matrix metalloproteinases form a large family of Zinc and Calcium-dependent proteolytic enzymes involved in cell growth and proliferation, reproduction, embryonic development as well as in the physiologic and pathologic tissue remodeling process through the lysis of the intercellular matrix.

The MMP family includes the conventionally secreted and membrane-linked MMPs as well as the sheddases (also known as ADAMs - a disintegrin and metalloproteinase). (1) To this date 28 zinc-dependent proteases have been described, classified into interstitial collagenases, gelatinases, stromelysins, and membrane bound MMPs, based on their substrate specificity (2,3). Many of these endopeptidases have been initially identified by their over-expression in the tumor tissue. However

Corresponding author:

Stefan Patrascu, MD, PhD
Department of Surgery
University of Medicine and Pharmacy
Craiova, 1 Tabaci str, Craiova 200642
Romania
E-mail: stef.patrascu@gmail.com

there is growing evidence of the MMPs involvement not only in the tumorigenesis but also in cancer cell migration and in the metastatic process. (4,5)

In order to maintain a balance between proteolysis and proteosynthesis, specific MMP tissue inhibitors (TIMPs) are synthesized in the tissues. Although TIMPs are the best known inhibitors of MMPs, metalloproteinases activity is also regulated by a wide range of mechanisms. Besides the TIMPs expression, the transcriptional regulation of MMP expression and the activation of the zymogen form of MMP plays an important part in their overall expression and proteolytic activity.

During the last two decades studies have demonstrated that high level of MMP1, 2, 3, 7, 9, 13, and 14 is directly linked to the malignant cell invasion, metastasis, and poorer prognosis (6-10). The expression and function of specific MMPs are, however, connected to the subtype and stage of tumor (3).

Objective

Of all these proteolytic enzymes, MMP 9 is of particular interest in oncology, as it shows the archetypal activity of MMPs. MMP 9 is a 92 kDa type IV collagenase, whose proteolytic action is essential for the mechanisms of neoplastic cell invasion in various malignancies: carcinoma (especially adenocarcinoma), lymphoma (Hodgkin disease and non-Hodgkin lymphoma) and sarcoma (osteosarcoma, fibrosarcoma and chondrosarcoma).

In the current study we are reviewing the expression of MMP 9 in some of the most frequent epithelial and lymphatic neoplasia of abdomen/pelvis localization, and its role as a prognostic factor for these types of cancer.

Methods for review

Data sources

The PubMed (US National Library of Medicine, National Institutes of Health - ncbi.nlm.nih.gov/PubMed) and Google Scholar databases were interrogated for articles published between January 1st, 1995 and July 31st, 2015 using the following search terms: "matrix metalloproteinase9", "MMP9", and "gelatinases", both as subject headings and keywords. We further narrowed our research for: "colorectal adenocarcinoma", "prostate adenocarcinoma", "ovarian carcinoma" and "lymphoma". The bibliography lists of the studies considered to be relevant were searched for further relevant papers. One additional paper was included due to the potentially important data offered and the paucity of relevant studies available on that specific topic (comparative analysis of MMP expression in Hodgkin and non-Hodgkin lymphomas). (11)

Study selection

Every title and abstract was evaluated by at least two authors

who independently decided if the paper is qualified for inclusion. Disagreements were resolved after careful evaluation by all six authors.

Inclusion and exclusion criteria

We included all studies published as full texts in English, French and Spanish in the above mentioned interval investigating the expression of matrix metalloproteinase 9 in epithelial and lymphatic malignancies. Data from non-English language texts were assessed by the authors who were fluent in the specific language. We focused on the prognostic value of MMP9 whenever possible. The search was restricted to human population groups. Studies were excluded if they investigated non-malignant pathology and if population groups accounted for less than 20 subjects. Case report studies, reviews and meta-analysis were also excluded.

Results

The search examined 1489 publications of which 19 were selected in this review. A total number of 1523 patients were included. The oldest study was published in 1996. Sample size varied from 28 to 187, with an average of 84.61. The main objectives of the studies was to evaluate the expression and role of different biological markers in the pathophysiology, therapy and prognosis of different histologic types of cancer (n=19). The most commonly used molecular marker was MMP-9, which was determined in all selected studies (n=19), followed by MMP-2 (n=9) and TIMP-1 (n=7). A short description of the included papers is provided in *Table 1*.

Colorectal adenocarcinoma

A large number of studies has been conducted in order to evaluate the prognostic value of MMP9, showing controversial data. (12-14) One conclusion can, however, be drawn: higher expression of MMPs offer no direct relation to tumor stage, with some studies suggesting that higher MMP-9 expression is a marker of the greater invasive potential of the cancer as well as of the poorer prognosis. (15) In a retrospective analysis of 64 patients undergoing rectal resection for carcinoma, Svagzdys et al. assessed the expression level of two gelatinases (MMP-2 and MMP-9) and their inhibitors (TIMP2 and TIMP3). (16) The results indicated that lower expression of MMP9 in stromal cell and a higher expression in parenchyma correlates with a significantly higher mortality, indicating different pathophysiological response in the malignant tumor. These data are thus supporting an earlier hypothesis of Lubbe et al. claiming that stromal reaction to neoplastic cell proliferation is a protective self-defense mechanism of the surrounding tissues. (17)

It is thus essential to search for the source of MMP-9 secretion in the tumor in order to design effective therapies that do not impair with the local anti-tumor mechanisms. (17) Another important aspect that needs to be considered is the variations of MMPs, especially MMP-9, after oncologic

Table 1. Studies assessing the correlation between MMP 9 expression and prognosis in colorectal adenocarcinoma, ovarian carcinoma, prostate carcinoma and lymphoma

No	Author	Year	No of patients	Histologic type	Markers analyzed
1	Angenete et al.	2009	32	Rectal carcinoma	MMP-1, -2, -9, TIMP-1, uPA, PAI-1, TGF- β 1, calprotectin
2	Babichenko et al.	2014	63	Adenocarcinoma of the prostate	MMP-9 and TIMP-1
3	Brun et al.	2008	99	Serous and mucinous ovarian tumors	MMP-2, -7, -9, MT1-MMP, TIMP-1 and -2
4	Campos et al.	2013	148	Hodgkin lymphoma	MMP-9
6	Desmeules et al.	2015	100	serous ovarian carcinoma	TIMP-2, MMP-2, MMP-9
7	Hazar et al.	2004	64	Hodgkin, non-Hodgkin lymphoma	MMP-2, MMP-9
8	Lubbe et al.	2006	28	Colon carcinoma	MMP-9
9	Moran et al.	2005	95	colorectal cancer	MMP-9, MMP-2, TIMP-1
10	Reis et al.	2011	89	Prostate carcinoma	MMP-9, TIMP-1, RECK
11	Sakata et al.	2000	114	Adenocarcinomas, borderline tumors	MMP-2, MT1-MMP, TIMP-2, MMP-9, TIMP-1
12	Svagzdys et al.	2011	64	Rectal adenocarcinoma	MMP-9
13	Thaer et al.	2015	67	Hodgkin and Non-Hodgkin lymphoma	MMP-9
14	Trudel et al.	2010	187	Prostate carcinoma	MMP-9
15	Unsal Kilic et al.	2007	44	Locally advanced rectal carcinoma	MMP-9
16	Waas et al.	2002	73	Colorectal carcinoma	MMP-2, MMP-9
17	Wood et al.	1997	117	Prostate carcinoma	MMP-2, MMP-9, TIMP-1, TIMP-2
18	Zeng et al.	1996	71	Colorectal carcinoma	MMP-9 RNA
19	Davidson et al.	2002	68	Ovarian carcinoma	MMP-2, MMP-9, MT1-MMP, TIMP-2, VEGF, IL-8, bFGF

Abbreviations: MMP: matrix metalloproteinase; MT1-MMP: membrane-type 1-MMP; VEGF: vascular endothelial growth factor; IL-8: interleukin-8; bFGF: basic fibroblast growth factor

therapy for colorectal cancer. It seems that MMP-9 expression offers a strong correlation with tumor response in patients with locally advanced rectal cancer following preoperative chemo- and radiotherapy, with a similar pattern of expression is also shared by MMP-2. (18, 19)

Prostate adenocarcinoma

Prostate cancer is the most frequent type of cancer treated in Urology Departments and the fifth most common neoplasia in the world. (20) There are several studies investigating the expression of MMP-9, offering somewhat contradicting results. (21, 22) A comparative analysis of Reis et al. comparing the expression of MMP-9, TIMP-1 and RECK in benign prostate adenoma and prostate adenocarcinoma revealed significantly higher overexpression of MMP 9 and underexpression of RECK and TIMP in the carcinoma group. (23) Two recent studies of Bibichenko et al. evaluated the expression of this collagenase in prostate adenocarcinoma. Despite its important role in the lysis of Type IV collagen of the basement membrane, the expression of MMP9 in prostate adenocarcinoma seems to be decreased, with a weak negative correlation between the levels of secretory tumor cell MMP-9 and cellular proliferative activity. (24) However, when assessing the activity of TIMP1, an inhibitor of MMP9, a decrease in its expression could be observed. The pathogenesis of tumor proliferation is thus explained by the imbalance between MMP9 expression and that of TIMP1. (24)

Ovarian carcinoma

To this date there are only a few studies investigating the levels of MMP9 in ovarian cancer. Based on limited evidence

it seems reasonably to affirm that MMP-9 expression is significantly higher in ovarian adenocarcinoma than in benign ovarian tumors. (25) When comparing different histologic types of tumors, a higher epithelial gelatinase (including MMP2 and 9) expression was observed in serous versus mucinous ovarian tumor. (26) Moreover, the overall expression of tissue MMP 9 in the high-grade serous ovarian carcinoma seems to correlate with a high risk of death. (27, 28)

The mechanisms of the MMP9 overexpression in ovarian neoplasia are not entirely deciphered. One explanation offered by Zhou et al. points to the hepatocyte growth factor (HGF) which in conjunction with the epidermal growth factor (EGF) acts as a stimulus for a highly invasive tumor phenotype via the increased secretion of MMP-9. (29)

Lymphatic neoplasia

While all lymphomas are malignant neoplasms, there is a wide spectrum of clinical behavior, with some following an indolent clinical course and others behaving in an aggressive manner so it is important to know the relationship between MMP and lymphoproliferative neoplasia.

Hazar et al. investigated the role of MMP-2 and MMP-9 in Hodgkin's disease (HD) and non-Hodgkin's lymphoma (NHL). They analyzed the serum samples of 42 patients and compared them with healthy control, using an immunoassay method for the determination of MMP-2 and MMP-9 levels. The mean MMP-9 and MMP-2 levels were found to be increased in HD and NHL patients compared to the control group. There were no relation between MMP-2, MMP-9 levels and clinical characteristics of patients. This data suggest that MMP-9 levels could be used for differential diagnosis between benign diseases and lymphoproliferative neoplasia. (30)

Another study of Campos et al assessed the overall survival of young patients with classical Hodgkin Lymphoma (cHL). The study suggests that although the expression of MMP-9 by Hodgkin-Reed-Sternberg cells is not associated with disease-free survival, it is however linked to a reduction in overall survival. (31) A similar conclusion has been drawn in case of non-Hodgkin lymphoma, as the expression of MMP-9 was associated with higher aggressiveness and poor prognosis. (2)

When evaluated comparatively the MMP-9 expression in NHL was found to be higher than that in HD, though the difference not statistically significant. (11) The MMP expression seems to be different, varying to the grades of NHL, but without the level of statistical significance. Similarly in the case of HD there are minimal differences in MMP-9 levels between HD with mixed cellularity and nodular sclerosis type. Concerning the tumor grading, there were no correlations between MMP-9 expression and tumor invasion or histological subtype. (11) As a result MMP-9 may be of a particular interest as a marker for the progression of lymphomas.

Conclusions

Molecular insights of MMP 9 provides a better understanding of the pathophysiology of tumor invasion and metastasis. Clinical studies indicated that the expression of this biomarker in epithelial and lymphatic neoplasia is both an independent prognostic marker characterized by poor overall survival as well as a strong prognostic tool for patients undergoing surgical or adjuvant therapy.

Disclosure

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