Matrix metalloproteinases in urinary system tumors. Part II - Matrix metalloproteinases in urinary bladder carcinoma

Młynarczyk G.[1,2,A,B,D], Kudelski J.[2,C], Darewicz B.[2,E], Galewska Z.[1,E], Romanowicz L.[1,A,F]

1. Department of Medical Biochemistry, Medical University in Bialystok, Poland
2. Department of Urology, Medical University in Bialystok, Poland

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ABSTRACT

Matrix metalloproteinases (MMPs), also referred to as matrixines, provide a group of proteolytic enzymes. They belong to the family of endopeptidases that break down elements of the extracellular matrix, resulting in its continuous remodeling.

Their activity is regulated at multiple levels, while tissue inhibitors of metalloproteinases play a major role in this process. Metalloproteinases play a significant part in neoplastic processes due to their contribution to local tumor invasion, the formation of distant metastases, as well as to angiogenesis Urinary tract tumors pose a significant diagnostic and therapeutic challenge and their incidence tends to grow every year. The aim of this second part of the review is to describe the urinary system structure and function, and to highlight the contribution of matrix metalloproteinases to the development of urinary bladder tumors.

Keywords: matrix metalloproteinases, urinary tract tumors, urinary bladder carcinoma

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***Corresponding author:**
Grzegorz Młynarczyk
Department of Medical Biochemistry
Mickiewicza 2C
15-089 Białystok, Poland
Tel/Fax.: 48 857485578
e-mail: mlynarz36@yahoo.pl

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INTRODUCTION

The extracellular matrix and matrix metalloproteinases are described in part I.

Urinary system

Structure - Due to formation from the same primordium within the mesoderm germ layer, the urinary system connects with the genital system into one urogenital system.

The urinary system comprises: two kidneys; renal calices and renal pelvis located in the renal sinuses into which urine is collected; ureters; urinary bladder; and urethra, through which urine is evacuated from the bladder [1]. Kidneys are located in the retroperitoneal space, providing the largest organs in this space. Renal parenchyma may be divided into the cortex and the medulla. The glomerulus provides the origin of the nephron; together with Bowman's capsule it comprises the renal corpuscule that opens into the proximal convoluted tubule connected with the distal tubule by the loop of Henle. Eventually, the distal tubule opens into the collecting ducts. Two or three minor calices converge to form major calices that open into the renal pelvis without an apparent border. The ureter is a duct that transfers urine from the renal pelvis into the urinary bladder. The urinary bladder is a reservoir for urine with well-developed muscular tissue, usually arranged in bundles accompanied with elastic fibers [1].

Function of the urinary tract – The kidneys perform a particular role in the urinary system. There are four basic functions of kidneys. The regulation function maintains the volume, composition and pH of bodily fluids at a constant level. The excretory function is responsible for the elimination of metabolic waste products, such as urea, uric acid, sulphates, and phosphates. The endocrine function involves the production of hormones like renin, prostaglandins, erythropoietin, and 1,25-dihydroxycholecalciferol. The metabolic function enables the degradation of hormones and other biologically active compounds. The volume of blood that flows through a kidney provides 25% of the cardiac output. Renal blood flow and hydrostatic pressure are two main factors influencing the glomerular filtration rate (GFR). The glomerular filtration process consists of the extravasation of fluid from the vessel lumen to Bowman's capsule via the filtration membrane. The normal range of the GFR value is 90-160 mL/min. [2]. Other elements of the urinary system are necessary for urine flow and temporary storage.

REVIEW

Urinary system tumors – epidemiology, pathomorphology, management

The most common tumors of the urinary system include renal and bladder carcinomas. The incidence of malignant tumors of the urinary system has been increasing over the last two decades in all age groups, irrespective of gender. The risk of urinary system tumor increases with age, being four times higher in males than in females [3].

Urinary bladder carcinoma.

Over 90% of histopathological examination results of malignant bladder tumors indicate a transitional cell carcinoma diagnosis. It is the fourth most common cancer in men and the eleventh most common in women. It constitutes approximately 5% of all malignant tumors. According to data for 2010, bladder carcinoma was diagnosed in 4919 men and 1377 women in Poland. In the same year, the deaths of 2470 men and 641 women due to the disease were registered [3].

The histological malignancy of this cancer is classified on a two-grade scale: "low grade" and "high grade" [4].

Hematuria is the most common symptom of bladder cancer. However, its intensity is not indicative of tumor size or malignancy degree. Cystoscopy involving specimen sampling and transurethral lesion resection are examinations of the highest diagnostic value, as they enable assessment of a given lesion. In approximately 80% of patients, the carcinoma is of a superficial nature at the time of diagnosis, being limited to the mucosa or submucosa. A method suitable for the treatment of superficial tumors is the endoscopic therapy TUR-BT (transurethral resection of the bladder tumor), and then check-ups on a regular basis. Neoplastic lesions that infiltrate the muscular layer of the bladder wall require radical surgical therapy [5].

Systemic treatment is recommended when lymph node involvement is diagnosed, in the case of distant metastases, or in inoperable patients with locally advanced disease [6].

Matrix metalloproteinases in the course of urinary bladder carcinoma

The structure of the urinary bladder differs significantly from the parenchymal structure of kidney. Its functions, as a reservoir of urine and an organ that expels urine from the body, depend on well-developed muscular tissues comprising three muscle layers arranged in bundles. There are also elastic fibers running next to the muscle bundles that enhance the distensibility of the bladder wall. The urinary bladder is a much more homogeneous organ from a morphologic point of view than the kidneys. Compared with the kidneys, there are fever inconsistencies in the published results of studies on MMPs and TIMPs [7].

Collagenases: MMP-1, MMP-8, MMP-13, MMP-18

MMP-1 is expressed in neoplastic cells in both superficial tumors and tumors infiltrating the muscular layers of the urinary bladder. The highest content of MMP-1 was noted in high-degree, highly locally advanced tumors, which may indicate a leading role of this enzyme in the tumor progression process. However, no relationship between MMP-1 expression and patient survival has been demonstrated, while higher expression was noted in recurrence of the disease [8]. MMP-1 was also determined in urine. However, its presence was detected only in 26% of examined patients. This result indicates poor suitability of determination of the enzyme in diagnostics for bladder carcinoma [9]. Small amounts of MMP-1 were detected in the blood of those patients. The possible role of epidermal growth factor in the induction of MMP-1 in bladder carcinoma cannot be excluded [10].

Assessment of blood MMP-8 content in patients with urinary bladder carcinoma did not reveal any relationship between enzyme amount and degree of local advancement, malignancy, and the formation of distant metastases [11]. But this enzyme seemed to be one of the key factors responsible for the release of the apoptosis-inducing ligand [12].

Investigation of MMM-13 revealed its expression on the mRNA level, particularly in the borderline of muscular infiltration [13-15]. No correlations between this enzyme's activity in the course of bladder carcinoma and patient survival prognosis were found [14]. Expression of MMP-18 in bladder cancers and its effect on the course of the disease are unknown.

Gelatinases: MMP-2, MMP-9

Gelatinase A is produced by fibroblasts in direct contact with tumor cells. MMP-2 together with MMP-9 degrades pre-digested collagen of various types, including collagen type IV, a primary component of basement membranes. It has been demonstrated that MMP-2's activity in bladder carcinoma is higher than in normal tissue, and increases in line with the tumor's increase in aggressiveness and malignancy [11,16]. Some cytokines, such as fibroblast growth factor, are known to regulate MMP-2 expression. Blood MMP-2 concentration was similar in the patient group and healthy individuals [17]. High concentrations of circulating pro-MMP-2 and TIMP-2 in the blood were both associated with a better clinical course. Also, pro-MMP-2 content can be used as an independent prognostic marker of bladder cancer progression [18].

Expression of gelatinase B and its increased activity was demonstrated in urinary bladder tumor cells, as well as in stromal cells. However, no MMM-9 expression in normal epithelium has been found [19]. Kader and co-workers [20] found that genetic variations in MMP-9 were associated with overall and invasive bladder cancer risk. Other work on MMM-9 demonstrated no significant correlation with local advancement of the lesion. However, with higher blood concentration of MMP-9, a higher degree of tumor malignancy was found [21]. The potential usefulness of the determination of concentrations of both gelatinases in urine as a prognostic factor remains disputable [22,23].

Matrilysins: MMP-7, MMP-26

Matrilysins have the lowest molecular weight among all matrix metalloproteinases. MMP-7 has a wide range of action. It binds E-cadherin and is bound by the Fas receptor on the cell surface, resulting in apoptosis inhibition [24]. Moreover, MMP-7 activates the receptor activator of NFkB ligand, which induces osteolysis via osteoclast activation. The process plays a primary role in the formation of bone metastases [25]. Some increase in MMP-7 activity in the tissue, blood, and urine of bladder carcinoma patients was noted by Svatek and colleagues [26]. The suitability of using blood concentration determination various MMPs as prognostic factors was analyzed. Only MMP-7 determination may be used as a prognostic factor. However, its application warrants further studies [26]. MMM-26 seems to be of only small importance in the course of the neoplastic process in the urinary bladder [27].

Stromelysins: MMP-3, MMP-10, MMP-11

To date, no relationships between tissue expression of MMP-3 and the advancement of neoplastic processes and survival prognosis have been found [8,17]. Expression of MMP-10 (stromelysin 2) does not show any relationship with the advancement of bladder carcinoma [28], while expression of MMP-11 was significantly higher and positively correlated with the degree of tumor aggressiveness and malignancy [29].

Transmembrane and other metalloproteinases

MMP-14, also called MT1-MMP, enhances local invasion and formation of metastases via pro-MMP-2 activation. An increase of MMP-14 content in bladder tumor tissue, in comparison with normal tissue, was demonstrated [30]. Enhanced expression of MMP-14 seemed to be associated with a high degree of malignancy, aggressiveness, and survival prognosis. Also, MMP-15 expression was markedly higher in tumors with a higher degree of aggressiveness and malignancy [27]. To date, few papers concerning other transmembrane metalloproteinases and other MMPs have been published.

Tissue inhibitors of metalloproteinases: TIMP-1,-2,-3,-4

An increase in TIMP-1 expression in bladder tumor tissue, compared with normal tissue, was demonstrated [9]. Moreover, the value of TIMP-1 concentration in the blood and urine of those patients was associated with advancement and degree of tumor malignancy [31].

Expression of TIMP-2 was detected in urinary bladder tumor cells, as well as in stromal cells [32]. Expression of the inhibitor increased with advancement of the tumor and was associated with a higher risk of recurrence and shorter survival [31-33]. Possibly, this was related with the proliferation-inducing effect of TIMP-2 [34]. Similar results were obtained in studies on mice. They suggest TIMP-2's contribution as a factor enhancing the carcinogenesis process, despite indisputable evidence of its primary function as an MMP inhibitor [35, 36]. Interestingly, independent studies on plasma and serum demonstrated higher TIMP-2 concentrations for patients diagnosed with bladder carcinoma than in healthy individuals. But low TIMP-2 levels and low MMP-2:TIMP-2 complex levels correlated significantly with a poor prognosis [37]. Other studies demonstrated a high level of diagnostic sensitivity of urine TIMP-2 content in the course of bladder carcinoma [23,38]. However, the results require confirmation in further prospective studies.

Work on TIMP-3 demonstrated that the gene encoding the inhibitor, when methylated, may become a marker of bladder carcinoma progression [39]. There are no reports concerning the importance of TIMP-4 in the course of urinary bladder carcinoma.

CONCLUSIONS

Remodeling of the extracellular matrix occurs in numerous physiological and pathological conditions. Degradation of the matrix enables multiple processes, such as the proliferation, angiogenesis, and translocation of tumor cells.

Malignant tumors of the urinary system usually appear after the 50th year of life in both men and women, and their incidence tends to grow within the last decades. Due to the results of numerous studies on MMPs, the enzymes have become attractive molecules for use as biomarkers or new therapeutic targets. Matrix metalloproteinases have been extensively analyzed as possible prognostic factors in both renal and urinary bladder carcinomas.

Urinary bladder carcinoma is the most common cancer of the urinary system. Thus, early diagnosis is of great importance. However, invasive examinations remain the golden standard. Cytological examination of the urine has certain limitations due to low specificity in diagnosing low-invasive tumors. Studies on matrix metalloproteinases demonstrated that urine concentration determination of MMP-2 and MMP-9 may provide a novel, low-invasive method of early detection for urinary bladder carcinoma. However, the method cannot be used as the only test due to its low sensitivity.

In many cases of malignant tumors, increased activity of MMPs is associated with a poorer prognosis; but on the other hand, as a potentially adverse prognostic factor it may result in the acceleration and application of more intensive therapy in the future. Work conducted on this group of enzymes is focused on the invention of inhibitors for a particular metalloproteinase. However, its main goal is to develop a medicine that would act locally rather than systemically, as it would provide a targeted therapy offering protection to other tissues potentially exposed to such a medicine.

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Conflicts of interest

The authors declare no conflicts of interest.

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