Matrix metalloproteinases in urinary system tumours. 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 extracellular matrix, resulting in its continuous remodelling.

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 tumour invasion and formation of distant metastases, as well as to angiogenesis Urinary tract tumours pose a significant diagnostic and therapeutic challenge and their incidence tends to grow every year. The aim of this second part of review is to describe urinary system structure and function and to highlight the contribution of matrix metalloproteinases in the development of urinary bladder tumours.

Key words: matrix metalloproteinases, urinary tract tumours, 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

Extracellular matrix and matrix metalloproteinases are described in part I.

Urinary system

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

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

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

REVIEW

Urinary system tumours – epidemiology, pathomorphology, management

The most common tumours of the urinary system include renal carcinoma and bladder carcinoma. The incidence of malignant tumours of urinary system tends to increase within last two decades in all the age groups irrespective of gender. Risk of urinary system tumour increases with age, being four times higher in males than in females [3].

Urinary bladder carcinoma.

Over 90% of the results of histopathological examination of bladder malignant tumour indicate the diagnosis of transitional cell carcinoma. It is the fourth most common cancer in men and the eleventh most common cancer in women. It provides approximately 5% of all malignant tumours. According to data of year 2010, bladder carcinoma was diagnosed in 4919 men and 1377 women in Poland. In the same year, deaths of 2470 men and 641 women due to the disease were registered [3]. Histological malignancy of this cancer is classified in two-grade scale, "low grade" and "high grade" [4]. Haematuria is the most common symptom of bladder cancer. However, its intensity is not indicative of the tumour size or malignancy degree. Cystoscopy involving specimen sampling and transurethral resection of the lesion are examination of the highest diagnostic value as they enable assessment of given lesion. In approximately 80% of patients the carcinoma is of superficial nature at the time of diagnosis, being limited to mucosa or submucosa. A method suitable for treatment of superficial tumours is endoscopic therapy TUR-BT - transurethral resection of the bladder tumour, and then check-up on regular basis. Neoplastic lesions that infiltrate muscular layer of 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 reservoir of urine and organ that transfers urine from the body to the outside, depend on well-developed muscular tissue comprising three muscle layers arranged in bundles. There are also elastic fibres running next to the muscle bundles, that enhance distensibility of the bladder wall. The urinary bladder is a much more homogeneous organ from morphologic point of view than kidney. As compared to kidneys, there are fever inconsistencies in 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 tumours and tumours infiltrating the muscular layers of urinary bladder. The highest content of MMP-1 was noted in high-degree, highly

locally advanced tumours, which may indicate leading role of this enzyme in the tumour progression process. However, no relationship between MMP-1 expression and patient survival was demonstrated, while higher expression was noted in recurrence of the disease [8]. MMP-1 was also determined in the urine. However, its presence was detected only in 26% of examined patients. The result indicates poor suitability of determination of the enzyme in diagnostics for bladder carcinoma [9]. Small amounts of MMP-1 were detected in blood of those patients. 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 amount of the enzyme and degree of local advancement, malignancy and formation of distant metastases [11]. But that 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 mRNA level, in particular in the borderline of muscular infiltration [13-15]. No correlations between the activity of the enzyme in the course of bladder carcinoma and patient's 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 being in direct contact with tumour cells. MMP-2 together with MMP-9 degrade pre-digested collagen of various types, including collagen type IV, primary component of basement membranes. It has been demonstrated that MMP-2 activity in bladder carcinoma is higher than in normal tissue, and increases in line with the increase in aggressiveness and malignancy of the tumour [11,16]. Some cytokines, such as fibroblast growth factor, are known to regulate the expression of MMP-2. Blood MMP-2 concentration was similar of the patient group and of healthy individuals [17]. High concentration of circulating pro-MMP-2 and TIMP-2 concentration in 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 tumour cells, as well as in stromal cell. However, no MMM-9 expression in normal epithelium was 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, higher blood concentration of MMP-9, higher degree of tumour malignancy was found [21]. Potential usefulness of determination of concentration 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 wide range of action. It binds E-cadherin and is bound by Fas receptor on cell surface, resulting in inhibition of apoptosis [24]. Moreover, MMP-7 activates receptor activator of NFkB ligand, which induces osteolysis via activation of osteoclasts. The process plays a primary role in the formation of bone metastases [25]. Some increase of MMP-7 activity in tissue, in blood and in urine of bladder carcinoma patients was noted by Svatek and colleagues [26]. Suitability of the use of determination of blood concentration of various MMP as prognostic factors was analysed. Only MMP-7 determination may be used as a prognostic factor. However, its application warrants further studies [26]. MMM-26 seems to have only small importance in the course of 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 process and survival prognosis were 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 aggressiveness and malignancy of the tumour [29].

Transmembrane and other metalloproteinases

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

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

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

Expression of TIMP-2 was detected in urinary bladder tumour cells, as well as in stromal

cell [32]. Expression of the inhibitor increased with advancement of the tumour and was associated with higher risk of recurrence and shorter survival [31-33]. Possibly, it was related with proliferation-inducing effect of TIMP-2 [34]. Similar results were obtained in studies on mice. They suggest contribution of TIMP-2 as a factor enhancing the process of carcinogenesis, despite indisputable evidence of its primary function as MMP inhibitor [35, 36]. Interestingly, independent studies on plasma and serum demonstrated higher TIMP-2 concentration 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 poor prognosis [37]. Other studies demonstrated 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 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

Remodelling of extracellular matrix occurs in numerous physiological and pathological conditions. Degradation of the matrix enables multiple processes, such as proliferation, angiogenesis and translocation of tumour cells.
Malignant tumours of the urinary system appear usually after 50th year of life in both men and women, and their incidence tends to grow within last decades. Due to the results of numerous studies on MMPs, the enzymes became attractive molecules for the use of them as biomarkers or new therapeutic targets. Matrix metalloproteinases were extensively analysed 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 urine has certain limitations due to low specificity in diagnosing low-invasive tumours. Studies on matrix metallo-proteinases demonstrated that determination of urine concentration of MMP-2 and MMP-9 may provide a novel, low-invasive method of early detection of urinary bladder carcinoma. However, the method cannot be used as the only test due to its low sensitivity.

In many cases of malignant tumours increased activity of MMPs is associated with poorer prognosis, but on the other hand, as potentially adverse prognostic factor it may result in 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 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
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