Matrix metalloproteinases in urinary system tumours. Part I - Matrix metalloproteinases in renal cell carcinoma

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ABSTRACT

Extracellular 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 part of review is to describe extracellular matrix and matrix metalloproteinases and to highlight the contribution of matrix metalloproteinases in the development of renal clear cell carcinoma.

Keywords: Extracellular matrix, matrix metalloproteinases, urinary tract tumours, renal clear cell carcinoma

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INTRODUCTION

The aim of this paper is a review of current knowledge about matrix metalloproteinases in human urinary system tumours.

Extracellular matrix

Extracellular matrix (ECM), as a reservoir of water and electrolytes, surrounds cells combining them into tissues, and tissues into organs. It is responsible for such features of tissues as strength, flexibility or elasticity. Basic components of extracellular matrix include collagen various types, elastin, several proteoglycans and structural glycoproteins. Basement membrane that separates epithelial tissue from connective tissue provides a special layer of ECM. It is made mostly of collagen type IV and glycoproteins, such as laminin and nidogen. Degradation of ECM components occurs with the contribution of extracellular matrix metalloproteinases (MMPs). They are synthesised and secreted in the form of inactive zymogens (proenzymes) by most of cells in the human body [1]. Activity of metalloproteinases in precisely regulated at the stages of transcription, secretion from cells, activation, as well as by tissue inhibitors of metalloproteinases (TIMPs) that control MMP activities in extracellular space [2].

Matrix metalloproteinases - classification

According to current knowledge, 28 matrix metalloproteinases have been described, of which 23 ones have been found in the human organism. MMPs can be divided into 5 major groups. The first one includes so-called collagenases, such as MMP-1 (interstitial, fibroblast collagenase 1), MMP-8 (neutrophil collagenase 2), MMP-13 (collagenase 3) and MMP-18 (collagenase 4). Their primary function is degradation of fibrillar collagen type I, II and III [3]. Second group comprises gelatinases: MMP-2 (gelatinase A) and MMP-9 (gelatinase B). Their primary function is disintegration of pre-degraded and denatured collagen [4]. A specific feature of matrilysins (third group) is the absence of haemopexin domain. Matrilysins includes MMP-7 (matrilysin 1) and MMP-26 (matrilysin 2). These enzymes degrade various ECM components, as well as molecules present on cell surface [5]. The fourth group comprises stromelysins: MMP-3 (stromelysin 1), MMP-10 (stromelysin 2) and MMP-11 (stromelysin 3). Among them MMP-3 exhibits the strongest proteolytic activity, as well as the ability to activate some inactive forms of metalloproteinases – zymogens [6].

Six transmembrane metalloproteinases (MT-MMP) comprise the fifth group. Four of them are classified as type I membrane proteins, MMP-14, MMP-15, MMP-16 and MMP-24, while remaining two (MMP-17 and MMP-25) are attached to the membrane by glycosylphosphatidylinositol molecule. The enzymes degrade various ECM components [7].

Other matrix metalloproteinases has not been classified to any of the above-mentioned groups. MMP-12 (metalloelastase) is expressed mostly in macrophages and is responsible for their migration. Apart from elastin, it degrades numerous other proteins [8, 9].

MMP-20 (enamelysin) degrades amelogenin, occurring originally in enamel [10]. MMP-22 was isolated from chicken fibroblasts. Its function remains unknown [11]. MMP-23 is expressed mostly in reproductive cells [12]. MMP-28 (epilysin) is one of the most recent discoveries in metalloproteinase family. Its expression in damaged skin by keratinocytes suggests that MMP-28 may be involved in skin repair process [13].

Matrix metalloproteinases – structure

MMPs are enzyme family with specific feature - multi-domain structure. Such elements of structure as pro-domain, catalytic domain, hinge region and haemopexin domain can be identified. The pro-domains structure of MMP-1, MMP-2, MMP-3 and MMP-9 has been well determined. That region contains so-called „cysteine switch" - a ligand responsible for the inhibition of the enzyme activity [7]. The catalytic domain is responsible for the course of catalysis. It is formed by a polypeptide moiety comprising five beta-sheets, three alpha-helices and connecting loops [14].

The name of next domain refers to haemopexin - a haeme-binding and transporting protein. The domain consists of four beta-structured segments. Its presence is vital for the catalytic domain's ability to degrade collagen triple helix [15]. That domain is absent in MMP-7, MMP-23 and MMP-26 [16]. The hinge region provides a connection between catalytic and haemopexin domain. It comprises 15-65 amino acid residues and maintains stable structure of the enzyme [17]. General overview of extracellular matrix metalloproteinase structure is given in Figure 1 [18]. Detailed domain structure of particular metalloproteinases is described by Jung and Zimowska [19].
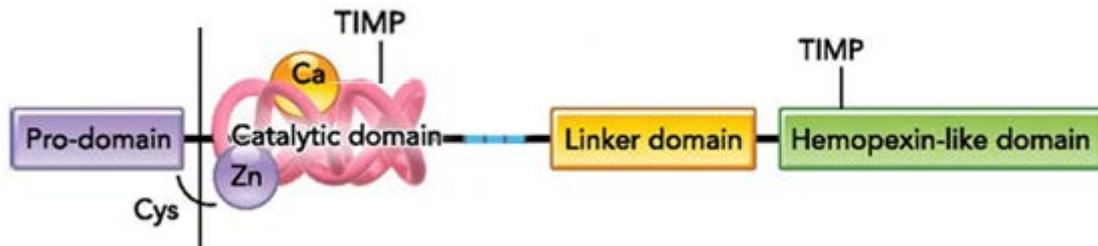
Figure 1. Scheme of domain structure of matrix metalloproteinases and binding sites of tissue inhibitors of metalloproteinases [18]

MMP synthesis and regulation of their activity

Metalloproteinases are synthesised by the majority of the human body cells, mostly connective tissue cells, leucocytes, macrophages, vascular endothelial cells, as well as tumour cells [20]. Newly synthesised metalloproteinases are available in the form of inactive zymogens (pro-MMPs) that include specific pro-peptide, called also pro-domain, in their structure. Proteolytic cleavage of the pro-peptide results in the exposure of active site, leading to transition of zymogen into active form. The enzyme activation may by mediated by trypsin, chymotrypsin, plasmin, furin, elastase and other MMPs (-1,-2,-8,-9) [21].

There are three stages of regulation of proteolytic activity: transcription and secretion, proenzyme activation and activity inhibition by specific tissue inhibitors [22]. Transcription is controlled by numerous cytokines. It determines cellular content of enzymatic protein. Secretion of pro-enzymes from cells is stimulated by numerous factors, including epidermal growth factor, vascular endothelial growth factor, tumour necrosis factor alpha and interleukin 1. On the other hand, their secretion is inhibited by steroid hormones and transforming growth factor beta [23]. Metalloproteinases are usually activated outside cells. Only some MMPs can be activated inside cells, within Golgi apparatus [21].

Tissue inhibitors of metalloproteinases - TIMPs

TIMPs are metalloproteinase-specific inhibitors. They bind to MMPs in 1:1 stoichiometric ratio. They create coordinate bonds, stable but reversible. To date four tissue inhibitors of metalloproteinases have been described: TIMP-1, TIMP-2, TIMP-3 and TIMP-4. Inhibition of MMPs activity by TIMPs prevents too extensive degradation of extracellular matrix and provides appropriate amounts of the matrix components and equilibrium of extracellular space processes. Pathological processes are associated with fluctuating but usually high MMP activity, and any changes in TIMPs amount are considered significant as they directly alter the degree of metalloproteinase activity. Inhibition of MMPs

activity by TIMPs is of particular importance in neoplastic process, resulting in the restriction of tumour growth, angiogenesis and metastasising. TIMP-3 also has proapoptotic activity [2,7,24], while TIMP-1 and TIMP-2 exhibit antiapoptotic activity [25]. TIMPs can be bound to metalloproteinases within catalytic and/or haemopexin domain, as shown on Figure 1.

Effects of matrix metalloproteinases

Despite the ability to degrade molecules adhered to cell surface, the primary function of MMPs is the degradation of extracellular matrix components: collagens, elastin, protein core of proteoglycans and structural glycoproteins, such as fibronectin or laminin. The ECM degradation facilitates migration of cells. As a consequence of the above-mentioned process, other components stored in the extracellular matrix may be released, such as some peptide growth factors. The process in general is referred to as extracellular matrix remodelling [26]. The activity of MMPs is significantly increased in the course of numerous pathological conditions, as compared to normal level, which markedly enhances the remodelling [26].

MMPs play very important role in neoplastic processes. Studies on mice have shown that reduction in metalloproteinase activity is associated with the restriction of tumour growth, as well as with lower risk of metastases [27, 28]. On the other hand, the increase in metalloproteinase activity is associated with the risk of progression of neoplastic process [29, 30]. Degradation of basement membranes by gelatinases that are only metalloproteinases able to degrade basement membrane collagen (type IV) may result in the formation of distant metastases. One of the features of metastatic process is its multi-stage nature, where loosening of intercellular junctions and the release of individual tumour cells provides the first stage. Next stage involves degradation of ECM and basement membranes, and migration of cells that penetrate to blood or lymph. Then adhesion to endothelial cells and secondary growth in new metastatic site occurs. MMPs play certain roles in all the stages [31].

Damage to basement membranes of blood vessels also enables migration of vascular

endothelial cells and, consequently, formation of new vessels. The most important role in angiogenesis is attributed to MMP-9, and then to MMP-2 and MMP-3 [32]. Growth factors released after degradation of ECM components accelerate tumour growth processes [33].

Tumour cells are stimulated for MMP synthesis by interleukins and growth factors. MMP-7 is a primary metalloproteinase produced by cancer cells. Equilibrium between proliferation and apoptosis is necessary for maintaining tissue homeostasis. Programmed cell death is triggered via surface cellular receptors, such as Fas. Fas receptors activate a cascade resulting in cell disintegration. MMP-7 degrades Fas-ligand and Fas-receptor on the surface of tumour cells, preventing their death [34].

URINARY SYSTEM IS DESCRIBED IN PART II.

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 [35].

Renal cell carcinoma

Renal cell carcinoma (RCC) provides over 90% of all malignancies of kidney, being the sixth most common cancer in men and the seventh most common cancer in women in Poland. RCC provides 2-3% of all the malignant tumours [35]. Incidence of this particular cancer increases every year, which may result from both higher „oncological vigilance" among primary care doctors and higher availability of imaging examinations. Peak incidence is between 60th and 70th years of life. According to the National Cancer Register data, there were 4644 new RCC cases and 2528 deaths due to RCC in Poland in the year 2010 [35]. Grade of the cancer is classified according to International Society of Urological Pathology scale, which includes four grades: G1, G2, G3 and G4. The higher the grade (G) number, the higher the degree of tumour malignancy (aggressiveness) is. Renal cancers are asymptomatic for a long time. Thus, over 50% of renal tumours are detected in ultrasound or Computed Tomography scan performed due to other indications. Surgery is the primary method of management in patients with diagnosed renal cancer. In patients not suitable for surgery systemic palliative therapy is administered. Earlier, any adjuvant therapy had not been effective. But the field of metastatic renal cell carcinoma has

significantly changed over the last year with Food and Drug Administration approvals of 3 agents. Medical management remains the mainstay of treatment for metastatic kidney cancer. Adjuvant therapy remains highly controversial, with some evidence that high risk patients may benefit from adjuvant therapy with Sunitinib [36]. Embolization of vessels supplying the tumour can be performed to relieve symptoms in patients not suitable for surgery. Patients with small tumours may remain under watchful waiting, and if progression occurs, local treatment is applied [37,38].

Matrix metalloproteinases in the course of renal carcinoma

Kidneys, as parenchymal organs, contain very low amount of connective tissue. Content of extracellular matrix is lower, as compared with other organs. Presence of metalloproteinases was detected primarily in glomeruli, as well as in proximal tubules, loop of Henle, distal tubules and collective ducts. Studies on mutual relationships between extracellular matrix components, activity of metalloproteinases and content of tissue inhibitors in renal tumours usually demonstrate the increase in MMP activity and reduction in TIMP content in the course of neoplastic process. Certain inconsistencies in particular studies may result from the determination of MMP content directly in tumour tissue specimen or determination of MMP content and activity and TIMP content in the blood or urine of renal tumour patients. The differences in MMP and TIMP content may also result from heterogeneous structure of the tumour itself [39].

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

The assessment of MMP-1 revealed its higher expression in tumour cells as compared to stromal cells [40]. Increased expression of MMP-13 was noted in cases of RCC with bone metastases. Simultaneously, certain role of transforming growth factor in the induction of the metalloproteinase expression was demonstrated [41]. Studies on neutrophil collagenase and MMP-18 in clear cell renal cell carcinoma did not demonstrate any increase in their activity in primary tumour tissue or metastases as compared to normal tissue [3, 32].

Gelatinases: MMP-2, MMP-9

An increase in the expression of gelatinases in tumour cells in patients diagnosed with renal carcinoma was demonstrated. It was even suggested that the determination of MMP-9 activity can be prognostic factor in cases of renal carcinoma [42]. Kallakury with colleagues [43] indicated the relationship between increased expression of MMP-2 and MMP-9, and disease progression and poor prognosis. Moreover, certain relationship between increased expression of the studied

metalloproteinases and higher stage in TNM - Tumor Nodus Metastases staging system [44] was demonstrated. However, other authors did not note any significant relationship between expression of gelatinases and degree of tumour malignancy [45].

Matrilysins: MMP-7, MMP-26

A study involving 156 patients, who underwent radical nephrectomy due to RCC, was focused on the assessment of matrilysin 1 in relation to the aggressiveness and malignancy of this tumour. A significant increase in expression of MMP-7 in tumour cells and blood vessels involved with neoplastic process was demonstrated. The level of expression was positively correlated with the degree of development of new vessels in the tumour area, local advancement and formation of distant metastases [46]. To date, there are no literature reports concerning MMP-26 in renal cell carcinoma. Study on the activity of metalloproteinases in the course of RCC demonstrated an increase in MMP-7 activity associated with the decrease in content or complete lack of products of extracellular matrix degradation in the urine [47]. However, other authors' observations were completely contrary [48]. Thus, the potential usefulness of determination of urine MMP activity as a prognostic factor in renal carcinoma remains disputable.

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

The increase in the expression of MMP-3 in tumour cells, that was positively correlated with increased expression of MMP-1, was demonstrated [40]. MMP-10 was assessed in a study involving 103 patients, who underwent radical surgery due to RCC. The presence of MMP-10 was detected in the cytoplasm of tumour cells in 45 patients. It was associated with both local aggressiveness and degree of malignancy of the tumour, while its expression was not correlated with the tumour size. MMP-10 is considered to be a potential therapeutic target to inhibit invasion and metastases of renal cell carcinoma [49]. Studies on stromelysin 3 revealed close relationship between its increased activity and local advancement of renal tumour, lymph node involvement and formation of distant metastases [50].

Transmembrane MMPs and other matrix metalloproteinases

Transmembrane metalloproteinases, MMP-14,MMP-15 and MMP-16 were considered to be expressed to a significant level in the course of renal cell carcinoma in tumour-modified tissue and present in urine samples collected from the same patients [51]. MMP-17, MMP-24 and MMP-25 were detected in kidneys not involved with tumour process [39]. However, there is lack of published reports on their expression in renal cell carcinoma.

Concerning other metalloproteinases, it has been demonstrated that MMP-12 is expressed in renal cell carcinoma tissue [52]. To date, there is no published studies on MMP-19, MMP-20, MMP-23, MMP-27 and MMP-28 activity in renal tumours.

Tissue inhibitors of MMP: TIMP-1, TIMP-2, TIMP-3 and TIMP-4

Study on kidneys of healthy mice revealed small expression of TIMP-1 and somewhat higher expression of TIMP-2 and TIMP-3. TIMP-4 was not expressed in the studied organs. Increased amount of the inhibitors was noted primarily in glomeruli [53]. Studies on human kidneys showed that TIMP-3 was the most expressed inhibitor among the four inhibitors [54].

Research on tumour cells revealed an increase in the expression of TIMP-1 and TIMP-2, as compared to stromal cells. However, according to some reports such exact relationship cannot be observed in every case [40, 45]. It should be assumed that such inconsistencies in expression of MMPs and TIMPs depend on the location, that is tumour cells or stromal cells [54]. There are very little data available on the expression of TIMP-3 and TIMP-4 in malignant renal tumours.

Additionally, there is an interesting protein called S-phase kinase-associated protein-2 that is overexpressed in the course of neoplastic processes. The protein contributes to the formation of distant metastases. Research on that protein in renal carcinoma demonstrated that it stimulates expression of MMP-2 and MMP-9, while inhibits synthesis of TIMP-1 [55].

In summary, it can be concluded that most investigations used blood as a biological material. RCC changes expression and/or activity of most MMPs and their inhibitors. Both kind of them seem to be perspective targets in tumour treatment. The problem is local medicine action on tumour cells without changing general metabolism of human organism.

CONCLUSIONS

Malignant tumours of kidney are usually detected accidentally, in imaging examinations performed due to other reasons. Despite numerous studies concerning the role of metalloproteinases and their tissue inhibitors in the course of renal cell carcinoma, there are still some unresolved questions. Possible use of metalloproteinase determinations as early diagnostic markers of renal carcinoma is problematic due to issues related to the result interpretation. MMP and TIMP content may be determined in tissue material or in blood or urine collected from patients. Some problems also are related to morphological heterogeneity of renal cell carcinoma that poses problems for a pathologist

assessing tissue specimen. Relative small size of the samples studied and lack of multifactorial analysis pose a significant obstacle to draw and formulate definite conclusions.

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Conflicts of interest

The authors declare no conflicts of interest.

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