

# Matrilysins and Stromelysins in Pathogenesis and Diagnostics of Cancers

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**Abstract:** Matrix metalloproteinases (MMPs) are endopeptidases which are widely studied in terms of their role in the physiological and pathological processes in the organism. In this article, we consider usefulness of matrilysins and stromelysins in pathogenesis and diagnostic of the most common malignancies in the world, e.g., lung, breast, prostate, and colorectal cancers. In all of the mentioned cancers, matrilysins and stromelysins have a pivotal role in their development and also may have diagnostic utility. Influence to the cancerous process is connected with specific dependencies between these enzymes and components of the extracellular matrix (ECM), non-matrix components like cell surface components. All the information provided below allows to take a closer look at matrilysins and stromelysins and their functions in the cancer development.

**Keywords:** metalloproteinases, matrilysin-1, matrilysin-2, stromelysin-1, stromelysin-2

## Introduction

Matrix metalloproteinases (MMPs) are a family of secreted and membrane-bound zinc-dependent endopeptidases that have the capacity to degrade the components of the extracellular matrix (ECM), but also non-matrix components. However, MMPs show apparent differences in substrate specificity, cellular and tissue localization, membrane binding and regulation. MMPs can be divided into 7 groups: collagenases, gelatinases, metalloelastases, stromelysins, matrilysins, membrane-type MMPs (MT-MMPs), and other MMPs. Scientific literature also suggests the division of MMPs into 8 groups, according to structural similarities and function: minimal domain MMPs (MMP-7 and MMP-26), simple hemopexin MMPs (eg MMP-3, MMP-10), gelatin binding MMPs (MMP-2 and MMP-9), furin-activated MMPs (MMP-11 and MMP-28), vitronectin-activated MMPs – MMP-21, transmembrane MMPs (eg MMP-14, MMP-15), GPI-anchored MMPs (MMP-17 and MMP-25) and type II transmembrane MMPs – MMP-22.<sup>1</sup>

All MMPs possess a polypeptide and a catalytic domain which is structurally highly similar. The molecule of MMPs generally consists of a propeptide, a catalytic domain, a linker peptide of variable lengths and a hemopexin (Hpx) domain (except MMP-7, MMP-26 and MMP-23 which have lack of the linker peptide and Hpx domain). The MMPs propeptide contains the PRGXPDP “cysteine switch” motif. Cysteine from the “cysteine switch” motif interacts with the zinc ion at the catalytic site of the enzyme, which blocks its activity. The catalytic domains have the zinc-binding motif HEXGHXXGXXH, in which the 3 histidine residues attach the zinc ion.<sup>2,3</sup>

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Generally the MMPs are secreted into the extracellular environment as inactive proenzymes (proMMPs). ProMMPs are converted to the active forms by proteolytic removal of the propeptide.<sup>4</sup> Activation occurs as a result of cysteine switching disruption.<sup>2</sup> The extracellular activation of most MMPs can be initiated by activated endopeptidases or serine proteinases that can cleave peptide bonds within the MMP prodomains. MMPs can be activated *in vitro* by chemical agents like HgCl<sub>2</sub> and N-ethylmaleimide, SDS, oxidized glutathione, chaotropic agents, reactive oxygen species (ROS), but also by heat treatment and low pH.<sup>5</sup> The activity of MMPs is slightly marked or negligible in homeostasis and it is regulated under gene expression, compartmentalization, proenzyme activation and inactivation. Expression of MMPs is transcriptionally controlled by cytokines, chemokines, growth factors, hormonal stress, cell-cell and cell-ECM interactions, bacterial endotoxin and oncogenic transformation. MMPs are a versatile family of enzymes with a multitude of physiological functions.<sup>3,6,7</sup> MMPs expression could be promoted by soluble form of E-cadherin highly expressed in cancer patients. Disruption of E-cadherin on cell surfaces is characteristic for Epithelial-to-Mesenchymal Transition (EMT) which has a pivotal role in tumorigenesis, metastases and chemoresistance of tumor. Cell-cell adhesion and maintenance of epithelial tissue integrity is mediated by E-cadherin. E-cadherin is connected with actin cytoskeleton through binding  $\alpha$ -,  $\beta$ -, and  $\gamma$ -catenins. Released catenins from E-cadherin/catenin complexes and translocation catenins to the nucleus are connected with changes in cell morphology and malignancy. E-cadherin aberrations are promoted by a various factors like, e.g., MMPs expression which suggest that MMPs expression promotes metastases and tumor progression.<sup>8</sup>

In this article we want to describe matrilysins and stromelysins in the most common diagnosed cancers in the world: lung, breast, prostate, and colorectal cancers.<sup>9</sup>

## Matrilysins

Matrilysins-matrilysin-1 (MMP-7) and matrilysin-2 (MMP-26) are the smallest of the MMPs. They have similar structural features – they are built only by the propeptide and catalytic domains.

Matrilysins have a wide substrate specificity against protein components of ECM, basement membranes and cell surface molecules. This broad degrading activity is

pivotal to the tissue-remodeling processes associated with physiological and pathological processes.<sup>10,11</sup>

## Structure and Function of MMP-7

Nowadays, MMP-7 is the smallest human metalloproteinase (28-kDa proenzyme, 19-kDa active form). As an inactive enzyme, MMP-7 consists of a propeptide and a catalytic domain, which means, activated enzyme comprises only catalytic domain.<sup>2,7</sup> It is secreted specifically by epithelial cells, some macrophages and by the tumor cells themselves. MMP-7 plays a crucial role in regulation of inflammatory reaction. MMP-7 takes part in degradation components of ECM, like casein, laminin, fibronectin, collagen III/IV/V/IX/X/XI, type I/II/IV/V gelatins, elastin and proteoglycans.<sup>12</sup> It also regulates biochemical process like an activation, degradation and shedding of non-ECM proteins alter their functions.<sup>7,13</sup>

MMP-7 plays a role in reepithelialization by shedding syndecan-1 which induces cell migration. Moreover, MMP-7 promotes inflammation by shedding syndecan-1/KC (CXCL8) complexes that allow neutrophil trans-epithelial movement and control their influx.<sup>14</sup> On the other hand, the interaction of MMP-7 with cell-associated syndecan-1/CXCL1 complexes limits the movement and activation of neutrophils, thus preventing destructive oxidative disruption on the surface of epithelial cells.<sup>15</sup> It also takes part in macrophage-mediated elastolysis. Data shows that macrophages under plasminogen free conditions, use metalloelastase (MMP-12) and gelatinase B (MMP-9) to degrade elastin. The presence of plasminogen stimulates macrophages to convert promatrilysin into active elastolysin via a pathway dependent on the urokinase type plasminogen activator. Moreover, the matrilysin-deficient macrophages fail to mediate an elastolytic response despite the presence of expression of MMP-9 and MMP-12.<sup>16</sup>

MMP-7 plays an important role in activation of epidermal growth factor receptor (EGFR) which is initiated by releasing an EGF ligand tumor growth factor (TGF- $\alpha$ ). TGF can synergistically activate with EGF and promote apoptosis in MMP-7 overexpressing cells.<sup>17,18</sup> EGFR binds to active soluble heparin-binding epidermal growth factor (sHB-EGF), which is formed also by MMP-7. MMP-7 cleaves heparin-binding epidermal growth factor precursor (proHB-EGF) into soluble mature sHB-EGF. All process is connected with CD44v3 which is a facultative cell surface proteoglycan implicated in cell adhesion and trafficking and which binds heparin-binding growth factors,

e.g., HB-EGF. Thus facilitates the interaction between transmembrane HB-EGF and docking to cell surface of MMP-7, which promotes cellular proliferation.<sup>19,20</sup>

Moreover, MMP-7 cleaves cell-surface proteins, such as membrane-bound Fas ligand (FasL) and E-cadherin which promotes cellular proliferation and invasiveness.<sup>13</sup> MMP-7 may promote tumor cells survival by cleaving FasL expressed in activated immune cells and tumor tissue. Fas is a member of the tumor necrosis factor and by its ligand (FasL) initiates the process of apoptosis by activation of Fas-associated death domain-like interleukin 1 $\beta$  converting enzyme or caspase-8. MMP-7 proteolytically cleaves FasL, thereby reduces cell surface FasL expression, thus the induction of apoptosis is decreased which protects cells against Fas-mediated cell death.<sup>21</sup>

E-cadherin is the epithelial adhesion molecule, which can be modulated in many ways including extracellular proteolysis. Research conducted by using nontransformed epithelial cell lines shows altered proliferation when E-cadherin is processed by MMP-7. E-cadherin cleaved by MMP-7 results in increased number of cells with enhanced migratory potential, but also increased proliferation which can regulate growth potential of nontransformed cells.<sup>22</sup> Zhang et al demonstrated in animal model that disruption in E-cadherin/ $\beta$ -catenin complex was connected with development and invasion of cancer. Interleukin-17 (IL-17) induced MMP-7 expression which cleaved E-cadherin/ $\beta$ -catenin complex and release  $\beta$ -catenin, thus enhancing EMT and tumor cell progression in prostate cancer (PCa). Data suggest that IL-17-MMP7-EMT axis can be a potential target for treatment this type of cancer.<sup>23</sup>

## MMP-7 in Carcinogenesis of Cancers

MMP-7 is produced by many types of cancer cells and it is affected in many processes in the tumor environment. In this chapter, we focused on expression of MMP-7 in lung, breast, prostate, and colorectal cancer.

### MMP-7 in Lung Cancer

High expression of MMP-7 was observed in non-small cell lung cancer (NSCLC) cells. Leinonen et al took into consideration the expression and prognostic value of MMP-7 in NSCLC. Expression of enzyme was assessed by immunohistochemistry staining in tumor cells and peritumoral stromal tissue and was compared to clinicopathological features. Presence of MMP-7 was noted more often in adenocarcinomas than in other histological types of cancer and was related with better tumor differentiation.

However expression of MMP-7 had no prognostic value in NSCLC patients.<sup>24</sup> On the other hand, Liu et al indicated the MMP-7 expression was significantly higher in squamous cell carcinomas than in adenocarcinomas. Moreover, they showed no difference in the MMP-7 expression in relation to apoptosis or angiogenesis. However, the overall survival was significantly lower in patients with positive expression of MMP-7 and regression analyses demonstrated MMP-7 status to be a significant prognostic factor.<sup>25</sup> Furthermore, data showed that specific concentration of MMP-7 might protect tumor cells from FasL-mediated death, by the inhibition of cell growth in a dose- and time-dependent manner by arresting in G0/G1 phase of the cell cycle and inducing apoptosis on A549 lung adenocarcinoma cell line.<sup>26</sup> However, MMP-7 shows potential to be an important factor in lung cancer progression.

### MMP-7 in Breast Cancer

Changes in the MMP-7 expression level in normal breast tissue may be associated with the development of neoplastic changes in breast.<sup>27</sup> In human, breast cancer (BC) cells expression of MMP-7 was significantly higher in comparison with normal mammary epithelium. The highest level of MMP-7 was found in high-grade tumors and in patients with moderate and poor prognosis. Finally, high levels of MMP-7 were significantly connected with a poor long-term survival.<sup>28</sup> MMP-7 immunoreactivity was detected in the cytoplasm of cancer cells, as well as, in normal epithelium adjacent to malignant epithelium.<sup>29</sup> It was proved that lymphoid enhancer binding factor-1 (LEF-1) was associated with regulation a gene encoding MMP-7 in BC cells. Detectable levels of both proteins were found in the highly metastatic BC cell line MDA-MB231 and in the non-invasive BC cell line MCF-7. Invasive BC according to the histological features can be classified into three groups: well differentiated (grade I, G1), moderately differentiated (grade II, G2) and poorly differentiated (grade III, G3). In addition, similar expression levels for MMP-7 and LEF-1 was observed in patients' primary cell cultures from invasive BC, stage G3. Moreover, LEF-1 siRNA decreased MMP-7 expression and inhibits cell proliferation after 48-h treatment of MCF-7 cells, which indicates that MMP-7 had important role in BC progression.<sup>30</sup>

### MMP-7 in Prostate Cancer

Elevated expression of MMP-7 mRNA in PCa was observed focally by gland epithelial cells. High levels of

MMP-7 was also noticed in anthropic glands that were surrounded by inflammatory-cell infiltrates. Moreover, MMP-7 expression was more frequently observed in neoplastic prostates than in normal tissue.<sup>31</sup> Lynch et al found in metastases of PCa to bone a significantly higher mRNA levels of MMP-7 at the tumor-bone interface in comparison to the tumor area alone. In addition, MMP-7 expression showed a good correlation with the bone destruction index. They also observed that MMP-7 was not expressed by PCa cells or in areas where osteoblastic changes were occurred, thereby suggested that the role of MMP-7 was connected to PCa induced osteolysis. This data indicated that MMP-7 played an essential role in the formation of bone metastases.<sup>32</sup> Additionally, it was shown that serum levels of MMP-7 in patients with PCa, healthy controls and patients with and without lymph node metastases had no statistical differences. Oppose to this, MMP-7 serum concentrations were significantly higher in patients with known distant metastases to bones. Thus, MMP-7 may be a potential marker to identify patients with metastatic PCa.<sup>33</sup>

## MMP-7 in Colorectal Cancer

Expression of MMP-7 was also observed in colorectal cancer (CRC) cells. Mimori et al elucidated the expression of MMP-7 and EGF in cancer tissue. There was a significant correlation between the incidence of positive MMP-7 expression and an activated EGF receptor. Furthermore, they found that the cancer tissue specimens stained with anti-MMP-7 antibody were almost identical to those stained by the activated EGF receptor antibody. This finding indicated that the phosphorylation of the EGF receptor occurred in CRC cells that had simultaneously accumulated MMP-7.<sup>17</sup> Patients samples with T1 stage of CRC (T1 stage is present when the cancer has grown through the muscularis mucosa into the submucosa) revealed connection between histopathological factors and elevated expression of MMP-7. MMP-7 expression by tumor cells at the invasive front was significantly correlated with venous invasion in T1 CRC. In addition, to evaluate changes in normal and invades veins, they were stained by Victoria Blue B staining, collagen IV staining. The ultrastructural alterations were examined using low vacuum-scanning electron microscopy (LV-SEM). In normal veins the structure of collagen IV had a strong and thick linear pattern. Examined by LV-SEM they were characterized by smooth bundles of elastic fibers in the adventitia and a mesh-like structure of

collagen fibers in the intima. In invaded veins both stainings were weaker, compared with normal veins. Under LV-SEM, they were characterized by an irregular surface that reflected the rupture of the two-layered structure of the vein. In addition, examination LV-SEM revealed that the thin part of collagen IV staining was characterized by partial disappearance of the mesh-like structure of collagen fibers in the intima and the cancer cells were visible within the altered layers of elastic and collagen bundles. However, MMP-7 expression was not significantly associated with tumor budding, lymphatic invasion, histological differentiation, growth type, morphology, desmoplastic reaction on the superficial layer, depth of invasion.<sup>34</sup>

## Summarizing

In all types of mentioned tumors data indicated that MMP-7 showed greater expression in cancerous tissue in comparison to healthy controls. In lung cancer, changes in MMP-7 expression were observed depending on the histological type of tumor and could be a prognostic factor. High expression of MMP-7 was significantly associated with a poor long-term survival in BC patients. In PCa, it has been noted that MMP-7 expression was associated with distant metastases. In CRC, MMP-7 expression was associated with infiltration of tumor cells into blood vessels, but no relationship was found between expression of this enzyme and the histological type of the tumor or lymph node metastases.

## Structure and Function of MMP-26

MMP-26 was discovered in 2000, by Park et al, in human endometrial tumor cDNA library (28 kDa inactivated enzyme; 19 kDa active form). It has a pro-domain with a unique cysteine switch sequence, PHCGVPDGS and a catalytic domain with the common zinc binding motif.<sup>35</sup>

MMP-26 hydrolyzes components of ECM, e.g., type IV collagen, fibronectin, fibrinogen and gelatin, as well as non-ECM proteins such as insulin-like growth factor-binding protein-1 ( $\alpha$ -1) and  $\alpha$ -1 protease inhibitor (also known as  $\alpha$ -1 antitrypsin,  $\alpha$ -1-PI).<sup>35,36</sup> Inactivation by MMP-26  $\alpha$ -1-PI, promotes serine proteinase activity, enhancing ECM degradation in pathological processes like cancerogenesis. IGFBP-1 is produced in liver and can bind specifically to IGF-1 and modulate its functions and bioavailability. Inactivation of IGFBP-1 promotes cell growth and survival by the increase of the effective insulin-like growth factor concentration in the surrounding medium.<sup>37</sup>



MMP-26 is able to activate MMP-9 which suggests that both MMP-26 and MMP-9 could act coordinately as part of a proteolytic cascade.<sup>36</sup> MMP-9 is one of the most-studied MMPs and plays pivotal role in many physiological and pathological processes. Thus an important role in ECM remodeling and membrane protein cleavage, it is found to be widely associated with cancer pathologies, e. g., tumor invasion, metastases and angiogenesis.<sup>38,39</sup>

$\beta$ -catenin releases from E-cadherin/ $\beta$ -catenin complexes may accumulate in the cytoplasm and translocate into the nucleus where it induces transactivation of genes (e.g., MMP-26) involved in the capacity of epithelial cells to acquire an invasive phenotype and cause EMT.<sup>40</sup> T-cell factor-4 (Tcf-4) motif and the activator protein-1 (AP-1) are the main regulators of the MMP-26 promoter. Studies show that Tcf-4 is only regulated by the E-cadherin and  $\beta$ -catenin pathway, which may affect the expression of MMP-26 in epithelial tumor cells. The cleavage of E-cadherin and  $\beta$ -catenin complexes facilitate the formation of Tcf-4- $\beta$ -catenin complexes. It is suspected that the Tcf-4- $\beta$ -catenin-E-cadherin axis function only in tumors of epithelial origin. Because Tcf-4 and AP-1 are transcription factors for the MMP-26 promoter, expression of this enzyme is mostly limited to cancer cells of epithelial origin.<sup>41</sup>

## MMP-26 in Carcinogenesis of Cancers

For the first time, MMP-26 expression has been demonstrated in endometrial cancer, thus there are many scientific reports about the role of this matrilysin in this type of cancer. However, literature data abound in scientific research into other types of cancers in which this enzyme plays an important role.

## MMP-26 in Lung Cancer

Data revealed by Li et al showed elevated expression of MMP-26 in atypical hyperplasia and NSCLC, with significantly higher expression in NSCLC than in atypical hyperplasia and normal tissue lung. Nevertheless, the difference was not significant between expression in atypical hyperplasia and normal lung tissues. The high expression rate of MMP-26 protein was significantly correlated to stage of disease and lymph node metastases, but not to age, gender, tumor size and differentiation.<sup>42</sup> The similar conclusions was found by Zhang et al where MMP-26 also was higher in cancerous tissue than in healthy tissue, and the expression levels of MMP-26 in lung cancer tissues were closely related to TNM stages, but were not related to age, sex, and tumor size.<sup>43</sup> However, multivariate

analysis showed that MMP-26 and stage were independent prognostic factors of NSCLC and the disease-free survival and overall survival were shorter in NSCLC patients with high expression of MMP-26 than in those with low expression of MMP-26.<sup>42</sup> In addition, research based on A549 cell lines, confirmed that MMP-26 contributed to NSCLC cells invasion and migration *in vitro*. Thus, MMP-26 may be served as a tumor marker in monitoring progression and predicting prognosis of NSCLC patients.<sup>44</sup>

## MMP-26 in Breast Cancer

It was observed that the expression levels of MMP-26 in human breast ductal carcinoma *in situ* (DCIS) were significantly higher than those in infiltrating ductal carcinoma (IDC), atypical intraductal hyperplasia and normal breast epithelia.<sup>45</sup> Data suggested that the enzymatic activity of MMP-26 in BC might be regulated by calcium concentrations in cellular systems. A human BC cell line, MDA-MB-231, transfected with wild-type MMP-26 cDNA showed a calcium-dependent invasive potential when compared with controls that were transfected with an inactive form of MMP-26. Analyses of sequence homology and the modelled MMP-26 structure indicated that cdMMP-26 may contain two possible binding sites with different calcium-binding affinities. It is important, because  $\text{Ca}^{2+}$  regulated of ECM degradation and cell invasion, therefore, enzymatic activity of MMP-26 might be regulated by calcium concentrations in cellular systems.<sup>46</sup> Research performed by Yang et al based on cell lines of BC MCF-7 transfected by pcDNA3.1(+)-neo expression plasmids carrying the proMMP-26 coding sequence, showed increased atypia, including unusual mitotic figures, glycogen pools and special lysosomes in the cytoplasm. The migration and invasion ability of MMP-26-transfected cells was increased in comparison with the control group, but markedly reduced in the presence of anti-MMP-26 antibody. MMP-26 also increased the malignant phenotype *in vivo*. The number of vessel branches and the total length of vessels induced by MMP-26-transfected cells were significantly expanded compared to those induced by non-transfected cells. Thereby, expression of MMP-26 may promoted BC invasion.<sup>47</sup>

## MMP-26 in Prostate Cancer

It was found that the expression of MMP-26 in human prostate carcinomas were significantly higher than those in prostatitis, benign prostate hyperplasia, and normal prostate tissues. MMP-26 was capable to activate pro-MMP-9 by cleaved at the Ala93-Met94 site of the pro-enzyme, and

this activation facilitated the efficient cleavage of fibronectin, promoting the invasion of PCa cells. To investigate the contribution of MMP-26 to cancer cell invasion via the activation of MMP-9, highly invasive and metastatic human PCa cell lines ARCaP were used. Data showed ARCaP cells express both MMP-26 and MMP-9 and using specific anti-MMP-26 and anti-MMP-9 reduced the invasiveness of ARCaP cells across fibronectin or type IV collagen. Moreover, the invasiveness of ARCaP cells was reduced by the introduction of MMP-26 antisense cDNA into these cells. These findings indicated that pro-MMP-9 activated by MMP-26 may contribute to human carcinoma cell invasion *in vivo*.<sup>48</sup> Cheng et al demonstrated the serum MMP-26 levels were significantly higher in PCa group than in benign prostate hyperplasia and control group. Similarly, the MMP-26 expression was positive in PCa tissues and negative in benign prostate hyperplasia tissues and control group. Summarizing, MMP-26 may be used as a diagnostic biomarker for identifying PCa patients from benign prostate hyperplasia patients and healthy individuals.<sup>49</sup>

## MMP-26 in Colorectal Cancer

Unfortunately, the clinical and pathological significance of MMP-26 expression in CRC tissue is still unclarified, thus the research literature is poor in this matter. Bister et al examined the cellular location and putative function of MMP-26 in normal, inflammatory and malignant conditions of the intestine. In healthy ileum, MMP-26 was seen in a linear pattern in the basal membrane zone. In colon, MMP-26 was found in healthy samples and inflamed samples, underneath the epithelium in the basal membrane area, but when the cells were migrating it was also present in the cytoplasm of epithelial cell. Interestingly, MMP-26 was not expressed around the crypts. In inflammatory bowel disease, MMP-26 was detected in migrating enterocyte, as well as in ulcerative colitis at the edges of gut wounds, where cells had migratory potential. These findings were opposite to Crohn's disease, where expression of MMP-26 in migrating cells was not observed. In CRC, expression of MMP-26 was observed between cancer islets in the matrix. No expression was demonstrated in the basal membrane or in the epithelium. These findings suggest that expression of MMP-26 in colon takes part in transformation of inflammatory tissue as well as cancerous tissue of the colon and may have a pivotal role in colon tissue homeostasis.<sup>50</sup>

## Summarizing

Higher expression of MMP-26 was observed in inflammatory and cancerous tissues. In lung cancer, MMP-26 expression was associated with TNM classification. Interestingly, high expression of MMP-26 in patients with lung cancer was associated with their shorter overall survival. In BC, a higher expression of MMP-26 was observed in cancer *in situ* than in infiltrative cancer or stromal glandular tissue. Studies in PCa cell cultures have shown that pro-MMP-9 activated by MMP-26 can contribute to the increase of invasive cancer cells *in vivo*. Expression of MMP-26 was demonstrated in healthy colon epithelium under the basal membrane, whereas in cells that acquired movement ability expression of MMP-26 was presented also in the cytoplasm, which may indicate the role of this enzyme in the migration of cancer cells.

## Stromelysins

All known stromelysins – stromelysin-1 (MMP-3), stromelysin-2 (MMP-10), stromelysin-3 (MMP-11) have the same domain arrangement as collagenases, but do not cleave interstitial collagen. Stromelysin 1 and 2 are closely related in structure and substrate specificity, but stromelysin 3 is distantly related. MMP-3 and MMP-10 have a similar substrate activity, e.g., cleave components of ECM and cell surface proteins, also take part in activation of other proMMPs by pro-peptide cleavage. However, MMP-11 have slightly marked ability to cleaving ECM components and is activated inside cells and secreted from cells as active enzyme.<sup>11,51</sup>

## Structure and Function of MMP-3

MMP-3 is expressed on wide range of cells including fibroblasts, macrophages, endothelial cells and epithelial cells, but also in various tumor cells.<sup>52</sup> It can degrade components of ECM, for instance, type III, IV, and V collagens; laminins; fibronectin; osteopontin; and proteoglycans.<sup>53</sup> Moreover, MMP-3 is involved in the shedding of protein ectodomains from the cell surface<sup>53</sup> and can also proteolytically activate other MMPs, e.g., MMP-1 and MMP-9.<sup>54</sup>

MMP-3 is secreted as inactive proenzyme (51-kDa) form which is activated in the extracellular space by proteases, notably plasmin,<sup>53</sup> and also can be activated by proteolytic removal of the prodomain by the serine proteases trypsin-2 and matriptase, to active form (43-kDa).<sup>2,55,56</sup> Active form of MMP-3 can hydrolyze some components of fibrinolytic

system such as fibrinogen, plasminogen and urokinase-type plasminogen activator (u-PA). Moreover, Lijnen et al reported specific cleavage of plasminogen activator inhibitor-1 (PAI-1) by MMP-3, resulting in inactivation of the inhibitor.<sup>57</sup> PAI-1 binds, for instance, vitronectin, a matrix protein that interacts with cell-surface integrins. The binding of PAI-1 to vitronectin blocks the vitronectin–integrin  $\alpha V\beta 3$  interaction, and regulates variety of cell activities including adhesion, migration, proliferation and survival.<sup>58</sup> Complex of PAI-1–vitronectin, may inhibit vitronectin–integrin complex, which mediates cellular responses in pathophysiological conditions like cardiac fibrosis,<sup>58</sup> but also in tumor progression thus promotion of angiogenesis in cancer tissue.<sup>59</sup> Data received by Lijnen et al showed that stable PAI-1 bounded to vitronectin was cleaved and inactivated by MMP-3, however, the cleaved protein did not bind to vitronectin. Cleave and inactivation of PAI-1 by MMP-3 may constitute a mechanism decreasing the antiproteolytic activity of PAI-1 and impairing the potential inhibitory effect of vitronectin-bound PAI-1 on cell adhesion or migration.<sup>57</sup>

MMP-3 also can promote EMT in mammary epithelium in cell culture and in transgenic mice by downmodulation of epithelial markers, and upregulation of mesenchymal markers. Proteolytic activity of MMP-3 is crucial factor that initiates the E-cadherin cleavage reaction and  $\beta$ -catenin translocation into the nucleus, resulting in loss of cell-cell contact. Moreover, MMP-3 induces the expression of an alternatively spliced form of Ras-related C3 botulinum toxin substrate 1 (Rac1b), thus causes increased level of ROS which induce oxidative damage to DNA, and stimulate EMT process by downregulation of epithelial cytokeratins and increased expression of mesenchymal markers including Snail, vimentin, and  $\alpha$ -smooth muscle actin.<sup>60,61</sup> Blavier et al provided evidence that MMP-3 was involved in the early stages of cancer transformation. Researchers used C57MG mouse breast epithelial cells in which they induced EMT via the Wnt1 signaling pathway. Overexpression of Wnt1 in C57MG cells was promoted EMT, by translocation of  $\beta$ -catenin from the cell membrane to the nucleus, affecting its transcriptional activity and thus cell proliferation and movement. In addition, Wnt1 overexpressing cells showed increased MMP-3 expression compared to normal C57MG cells, also the effect of Wnt1 on EMT was inhibited by MMP inhibitors. Furthermore, it was noted that MMP-3 and Wnt3a cooperated in increasing the transcriptional activity of  $\beta$ -catenin in C57MG cells. These results suggested that

MMP-3 is an important factor promoting the Wnt/ $\beta$ -catenin signaling pathway.<sup>62</sup>

## MMP-3 in Carcinogenesis of Cancers

MMP-3 expression is shown in many normal cells, but also in cancer cells. Due to the various mechanisms of action mentioned briefly above, MMP-3 may had influence on tumor progression and angiogenesis and thus affect disease development and patient survival.

## MMP-3 in Lung Cancer

Mehner et al evaluated the stromal and epithelial cell expression of MMP3 in lung cancer. In lung cancer specimens, they found MMP-3 staining primarily in the tumor cells, with much less MMP-3 staining in the surrounding stroma. They elucidated that expression of MMP-3 can serve as a prognostic marker for patient survival in lung cancer. Tumor expression of MMP3 was correlated with poor patient survival and earlier recurrence in this type of cancer.<sup>63</sup> The level of MMP3 expression can be influenced by single nucleotide polymorphisms (SNPs) in the promoter region of its gene. Fang et al hypothesized that the MMP-3 SNP may modified risk of the development and metastases of lung cancer and the MMP-3 SNP may worked with MMP-1 SNP to influence the development and progression of the tumor. Data showed that smoking patients with the MMP3 5A allele had an increased risk to develop NSCLC. Moreover, the MMP3 5A homozygote was significantly more frequent in patients with positive lymph nodes metastases than those without lymphatic metastases. Their result suggested that the MMP3 promoter polymorphism may modify susceptibility to NSCLC.<sup>52</sup> However, MMP-3-1171 5A/6A polymorphisms in patients with NSCLC had no influence to patients survival.<sup>64</sup> Studies Jiang et al showed that treatment by interleukin 6 (IL-6) induced ataxia-telangiectasia mutated activation contributed to multidrug resistance formation in lung cancer cells and facilitated lung cancer metastases via MMPs, such as MMP-3. MMP-3 was involved in IL-6 correlated cell migration, also IL-6 treatment increased MMP-3 expression and activity. Moreover, *in vivo* the inhibition of ATM phosphorylation efficiently abolished IL-6 up-regulating MMP-3 expression and inhibited ability of cancer cell migration.<sup>65</sup>

## MMP-3 in Breast Cancer

On the murine model spontaneous development of premalignant and malignant lesions in the mammary glands of

transgenic mice (CD-1) that express an autoactivating form of MMP-3 was observed. What's interesting these changes were absent in nontransgenic littermates. Thus MMP-3 can act as a natural tumor promoter and enhance cancer susceptibility.<sup>66</sup> In addition, analysis of the tumor tissue developed in MMP-3 transgenic mice revealed genomic changes in cancer cells, which may had influence to promotion tumor progression.<sup>67</sup> Promoter polymorphism of MMP-3 may have influence in BC risk. Ghilardi et al in a pilot study, evaluated the impact of MMP-3 5A/6A polymorphism on susceptibility and metastases in BC. The frequency of 5A allele was higher in the BC group than in controls. Furthermore, the 5A allele was more common in patients with metastases, at the time of diagnosis.<sup>68</sup> This results are in line with data received by Krippel et al which proved that MMP3 5A/6A promoter polymorphism may be connected with a higher risk for metastasizing among BC patients. In addition, in their studies homozygotes for the MMP3 5A/5A high activity genotype had a much higher percentage of lymph node metastases than carriers of other genotypes. However, the MMP3 5A/6A promoter polymorphism did not appear to influence BC susceptibility.<sup>69</sup> On the other hand, recent study indicate increased frequency of 6A allele of MMP-3 in BC patients. Additionally, the 2G-6A haplotype (alleles of MMP-1 and MMP-3 respectively) has shown more higher receptivity to BC, oppose to the haplotype 1G-5A (MMP-1 and MMP-3 respectively) frequency, which was increased in controls than in patients, thus may had a protective effect against BC. 5A/6A MMP-3 polymorphism was found to be significantly connected with lymph node metastases, which have influence to the survival rate of patients.<sup>70</sup>

## MMP-3 in Prostate Cancer

Jung et al elucidated blood plasma concentration of MMP-3 in PCa patients. They compared four groups of patients: healthy controls, patients with benign prostatic hyperplasia and patients with PCa with and without metastasis. The mean MMP-3 concentration was significantly higher in PCa patients with metastases compared with controls, benign prostatic hyperplasia and PCa patients without metastases.<sup>71</sup> Hsieh et al focused their attention on stromal fibroblasts during development of PCa. They used normal and PCa associated stromal fibroblasts (CAFs) derived from a co-culture cell model and clinical patient samples. Microarray analysis showed MMP-3 was decreased in CAFs, but was elevated in PCa cells. In epithelium of

prostate glands, MMP-3 staining was positive in tumor cells and elevated in comparison to normal tissue. In serum increased levels of MMP-3 was observed in patients with malignant cancer progression. The MMP-3 serum level in PCa patients with high-grade tumors and low-grade tumors was significantly higher than that in patients with benign prostatic hyperplasia. Moreover, research showed how tumor microenvironment modulates ECM homeostasis, showing the key role of ROS in switching MMP-3 expression in stromal fibroblasts and PCa cells during PCa progression.<sup>72</sup>

## MMP-3 in Colorectal Cancer

MMP-3 promoter polymorphism may be also connected with a CRC susceptibility. Hinoda et al showed the frequency of the promoter polymorphism 6A/6A having the lowest transcriptional level was notably elevated in patients with cancer than in controls in comparison to the 5A/5A and 5A/6A.<sup>73</sup> Research carried out on Iranian population indicated MMP-3 5A/5A genotype enhanced CRC cell invasion. Data showed the frequency of the 5A allele among CRC patients was significantly higher than in healthy group. Additionally, 5A/5A genotype was more frequent in patients with metastases.<sup>74</sup> Sipos et al attempted to find protein markers to identify changes in protein expression profile, focused on the passage from dysplasia to cancer in colorectal tumors, which is the most pivotal factor in the cancer progression and can elucidate path from the adenoma to the dysplasia and in consequence carcinogenesis in colon (adenoma–dysplasia–carcinoma sequence; ADCS). MMP-3 and C-X-C motif chemokine ligand 1 (CXCL1), showed a linear expression which was correlated with the ADCS and can distinguish dysplasia and early malignancy. At this basis, they found that high-grade dysplastic and early-stage CRC can be differentiated correctly by the stromal expression of MMP3 and CXCL1, respectively, on tissue microarray-based analysis. Moreover, the expression of the MMP3 protein in the lamina propria was highly specific in detecting cancer transition.<sup>75</sup>

## Summarizing

Higher expression of MMP-3 was observed in inflammatory and cancerous tissues. In lung cancer, MMP-3 expression was associated with poor patient survival and shorter remission times. Studies in animal models have shown increased expression of MMP-3 in mammary tumor tissue. It has also been noted that the MMP-3 promoter polymorphism may have an impact on the development of BC and metastases. Moreover, in patients with CRC was noticed a similar



tendency – the MMP-3 promoter polymorphism may by affected the development of this type of cancer. MMP-3 serum levels were higher in patients with PCa compared to healthy controls and patients with benign lesions.

## Structure and Function of MMP-10

MMP-10 is secreted as a 53-kDa proenzyme and is activated to a 47-kDa mature protease and has 82% sequence homology with MMP-3.<sup>2</sup> *In vitro*, it is able to degrade the protein core of proteoglycans, type IV and IX collagens, laminin-I, fibronectin, the globular domains of collagens I and III, elastin, gelatin and casein.<sup>76,77</sup>

MMP-10 is not expressed in fibroblasts, but is produced by epithelial cells like human basal keratinocytes. Expression of MMP-10 is induced by tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ), transforming growth factor  $\beta$ 1 (TGF- $\beta$ 1), EGF and TGF.<sup>77</sup> In HaCaT cells with induced EMT, was shown an increase in the expression of MMP-10 after stimulation with a combination of TGF-1 and EGF. Moreover, combination of both this cytokines caused excessive collagenolysis which altered the proteolytic balance in the microenvironment thus stimulated cell invasiveness by promoting motile behavior which is characteristic for EMT.<sup>78</sup> In hepatocellular carcinoma, MMP-10 contributed the growth of cancer cells by increasing the expression of C-X-C chemokine receptor type 4 (CXCR-4), stromal-derived factor-1 or the increase in transcriptional activity of the C-Jun protein, which results in EMT of liver cells.<sup>79</sup>

MMP-10 is also important factor in skin wound healing, e.g., by stimulation of keratinocytes migration.<sup>76,77</sup> Research based on animal model showed that MMP-10 enhanced migration of cultured keratinocytes, but in the other hand revealed abnormalities in the organization of the wound epithelium *in vivo*. Overexpression of a constitutively active MMP-10 mutant in the epidermis resulted also degradation of newly formed matrix, e.g., laminin-5, which probably enabled cellular migration, partial loss of cell–cell contacts of the migrating keratinocytes and an increase rate of apoptosis of wound edge keratinocytes.<sup>76</sup> Moreover, in response to injury, MMP-10 is induced by epithelial cells and macrophages in many organs, but its functions in wound repair are still unknown. In wound exist two types of macrophages: proinflammatory macrophages (M1), and remodeling-competent macrophages (M2). MMP-10 controls M2 collagenolytic activity without affecting collagen production by fibroblasts. Although, it promotes collagen turnover by

macrophages by enhancing the expression of specific metallocollagenases, e.g., MMP-13, MMP-8.<sup>80</sup>

Meyer et al showed that PKC/p53-resistant cells express a higher level of several MMPs, including MMP-10. The p53 protein is responsible for the proper course of the cell cycle, DNA repair and apoptosis, depending on the phosphorylation status. The family of protein kinase C (PKC) isozymes affects p53 functions, and is involved in the cell cycle and programmed cell death. Data provided evidence that PKCs was able to potentiate p53-induced apoptosis and that MMP-10 expression provided partial protection against proapoptotic PKC/p53 signals.<sup>81</sup>

## MMP-10 in Carcinogenesis of Cancers

MMP-10 is produced by epithelial cells, thus its role in tumors originating from epithelial tissue is significant. Under the influence of various factors, ie cytokines, it can lead to disturbances in the cell microenvironment and thus cause effects in cells leading to the development of cancer through for example EMT.

## MMP-10 in Lung Cancer

MMP-10 protein was detected at low levels in normal human lung tissues and at notably higher levels in all types of NSCLC. It was proved that MMP-10 expression was mainly present in the tumor mass, in comparison to the tumor stroma. Gill et al observed no relationship between MMP-10 activity levels and clinicopathological characteristics in NSCLC patients, and also no correlation was observed between MMP-10 protein expression and tumor type, stage or lymph node invasion. However, presented data showed that MMP-10 expression and activity were notably higher in all NSCLC histological types oppose to histologically normal lung tissues and could be a potential target for the development of novel therapies against this type of cancer.<sup>82</sup> Frederick et al demonstrated that atypical protein kinase C $\iota$  (PKC $\iota$ ) is an oncogene in NSCLC. PKC $\iota$  promoted growth and carcinogenicity of NSCLC cells through the Rho family GTPase, Rac1. In addition, transgenic overexpression of the domain PB1 of PKC $\iota$  in NSCLC cells inhibited Rac1 activity and transformation. The gold salt aurothiomalate (ATM) selectively inhibited the interaction of the PB1 - PB1 domain between PKC $\iota$  and Par6 *in vitro*. ATM blocked Rac1 activity and inhibited NSCLC cells growth, suggested the role of the PB1 – PB1 domain interaction between PKC $\iota$  and Par6 in activating and transforming Rac1. Researchers also demonstrated the critical involvement of Par6 $\alpha$  in

NSCLC transformation and found that Par6 $\alpha$  was a key component of a PKC $\epsilon$ –Par6 $\alpha$ –Rac1 signaling axis which promoted growth and invasion of cancer cells. Moreover, they identified the MMP-10 as a crucial gene of the PKC $\epsilon$ –Par6 $\alpha$ –Rac1 signaling axis that was essential for growth and invasion of NSCLC cells. PKC $\epsilon$  and MMP-10 were overproduced in primary human NSCLC tumors, thus MMP-10 expression was predictive factor of poor survival of NSCLC patients.<sup>83</sup>

## MMP-10 in Breast Cancer

Eiseler et al elucidated the influence of protein kinase D1 (PKD1) expression to MMPs in BC. Data suggested that PKD1 regulated the expression of MMPs in BC cells, for instance MMP-10, and the loss of PKD1 expression elevated their malignant potential. This mechanism may be due to the function of PKD1 as a negative regulator of MMP expression, which suggested that MMP-10 can be involved in progression of BC.<sup>84</sup> Espinoza-Sanchez et al carried out research based on Matrigel-based three-dimensional system, to analyze the inflammatory secretion profile of tumor cells of BC (cell lines MDA-MB-231 and MCF-7) individually or in co-culture with monocytes (cell line U937). They confirmed relationship between interaction of tumor cells and monocytes which promoted significantly unregulated expression of MMPs. Moreover, they tested primary tumor cells obtained from BC patients and analyzed their secretion profiles, both individually and in co-culture with primary monocytes and monocytic cell lines. Their study proved that recruitment of monocytes increased the aggressiveness of BC cells and stimulated them to secrete excessive levels of potent pro-inflammatory cytokines such as IL-8 and MMPs like MMP-10.<sup>85</sup> Köhrmann et al discovered stronger expression of MMP-10 in BC tissue compared to normal breast tissue. Expression of MMP-10 was connected to tumor grade, and it was higher in analysed G3 stadium compared to G2.<sup>86</sup> On the other hand research performed by Benson et al shows that expression of MMP-10 in BC tissue was downregulated in G2 and G3 in comparison to normal breast tissue.<sup>87</sup>

## MMP-10 in Prostate Cancer

The clinical and pathological significance of MMP-10 expression in PCa tissue is still clarified. Maruta et al tried to elucidate the role of MMP-10 in non-metastatic PCa. In specimen obtained by radical prostatectomy MMP-10 expression was examined using immunohistochemical technique. They investigated relationship between MMP-10

expression and clinicopathological features. MMP-10 was mostly detected in cancer cell cytoplasm, and in addition the proportion of MMP-10-expressing cancer cells was significantly higher than in healthy tissue. Similarly, in the pT scale, the proportion of MMP-10 positive cancer cells was notably higher in more advanced stage of tumor (stage pT3) and was correlated with blood vessel invasion. Multivariate analysis showed that MMP-10 expression was closely related to the pT stage. Additionally, they speculated that MMP-10 modulates tumor growth via the regulation of the balance of cell proliferation and apoptosis.<sup>88</sup> Singh et al showed that interactions between chemokine receptor CXCR5 and chemokine CXCL13 had an influence to the expression of MMP-10 in PCa. In cell lines of PCa cultured with or without CXCL13, changes in expression of MMP-10 was observed. A significant increase in MMP-10 mRNA expression and active protein was observed in the LNCaP cell lines after CXCL13 treatment. On the other hand, untreated PCa cell lines PC3 expressed higher levels of MMP-10 mRNA and active protein than untreated LNCaP cells. These data suggested that MMP-10 expression in PCa is dependent on CXCL13 and CXCR5 cooperation.<sup>89</sup>

## MMP-10 in Colorectal Cancer

Koller et al evaluated the role of MMP-10 in colonic tissue damage induced by dextran sulphate sodium (DSS) treatment. Used murine models, they investigated that absence of this enzyme leads to significantly worse disease scores and its pivotal for resolution of DSS-induced colonic damage. MMP-10 was produced by infiltrating myeloid cells in mice colitis, but also in human inflammation tissue. Researchers performed bone marrow transplant and confirmed hypothesis that cells of bone marrow derived MMP-10 were essential to colitis severity. MMP-10-negative mice were more likely to develop dysplastic changes in the colon after two rounds of DSS exposure. MMP-10 was vital factor to prevent chronic inflammation and in consequence dysplastic lesions in colon.<sup>90</sup> Moreover, data showed overexpression in sera of MMP-10 in CRC patients in comparison to healthy controls. Statistical analysis revealed a high levels of the enzyme showed significantly impaired overall survival in patients with colon tumor and may be an independent unfavorable prognostic marker in patients with CRC.<sup>91</sup>

## Summarizing

MMP-10 expression was higher in tumor cells compared to healthy tissues. In lung cancer, higher concentrations of

MMP-10 were observed in tumor tissue than in the surrounding stromal cells, although no association was found between TNM classification. In BC, MMP-10 expression was associated with higher tumor grade. Similarly, in PCA higher MMP-10 expression was observed in more advanced stage of tumor and the presence of infiltration on blood vessels. Overexpression of MMP-10 in the serum of patients with CRC was associated with a decrease in overall survival and may be an independent unfavorable prognostic marker.

## Structure and Function of MMP-11

MMP-11 gene expression was firstly described in the stromal cells surrounding the neoplastic cells of breast carcinomas. It is categorized as stromelysin, but MMP-11 similarity with MMP-3 is barely marked than between MMP-3 and MMP-10.<sup>92</sup> As was mentioned before, MMP-11 is distantly related with other stromelysins. MMP-11 is membrane bound MMPs, which is activated intracellularly by furin.<sup>11</sup> The 56-kDa proenzyme is secreted as a 47-kDa active protease.<sup>2</sup> MMP-11 cleavages collagen VI and non-structural ECM component substrates like  $\alpha$ -1 antitrypsin,  $\alpha$ -1 proteinase inhibitor and IGFBP-1.<sup>11,93</sup> It is connected with physiological processes like embryonic development, wound healing, but also with pathological processes, e.g., carcinogenesis.<sup>94</sup> In normal and pathological conditions MMP-11 is mainly expressed by fibroblasts. However, there are evidences that expression of MMP-11 is also occurred in tumor cells, as well as in surrounding them stromal cells.<sup>95</sup> During tissue remodeling, it was noticed that MMP-11 expression appeared much later than other MMPs. Therefore, it is assumed that in tumor processes MMP-11 does not participate in the initiation of basal membrane disintegration, however, it may be important in later transient tissue processes. Several reports indicates that MMP-11 is necessary for the development of cancer, it has no function with other MMPs involve in malignant processes. MMP-11 is not able to degrade any important ECM component, does not modify the proliferation or motility of epithelial cells and not appear to be proangiogenic or proapoptotic factor. MMP-11 exhibits anti-apoptotic properties by controlling proteinase activity or an inflammatory response, promoting epithelial cell growth under adverse conditions.<sup>96</sup> The mechanisms underlying these effects are unknown. MMP-11 is thought to degrade proteolytically unknown protein components that promote cell survival.<sup>2</sup> Anti-apoptotic properties of MMP-11 favor the development of the cancer

process, as well as, stimulation of migration and invasion of cancer cells, on the other hand studies in animal models show that MMP-11 can inhibit metastases. High concentrations of MMMP-11 were found in the sera of cancer patients. Increased expression was found in immunohistochemical samples of solid tumor tissue, however, slight expression was noted in normal tissue.<sup>93</sup>

## MMP-11 in Carcinogenesis of Cancers

MMP-11 can play both pro-cancer and anti-cancer roles. The mechanisms of both types of action are not fully understood and are based on speculation. It is known that increased MMP-11 expression is noted in cancerous tissues, whereas in healthy tissues MMP-11 expression is almost absent.

### MMP-11 in Lung Cancer

It is believed that MMP-11 may play a significant role in NSCLC. As mentioned before, MMP-11 had the ability to cleave  $\alpha$ -1 proteinase inhibitor. Deficiency of  $\alpha$ -1 proteinase inhibitor played a crucial role in the development of lung diseases. MMP-11 may indirectly promoted the destruction of the extracellular pulmonary matrix in NSCLC.  $\alpha$ -1 proteinase inhibitor can inhibit the ECM degradation via elastase mediated proteolysis, but MMP-11 can disturb this process. Research showed that transcript and protein of MMP-11 was more abundant in NSCLC stromal fibroblasts than in normal lung tissue.<sup>97</sup> It was shown MMP-11 may play a pivotal role in transition from lung preneoplasia to carcinoma. Bolon et al performed research based on hybridization and immunohistochemistry. They analyzed presence of MMP-11 in lung cancer tissue and compared obtained data with clinical and pathological parameters. MMP-11 was more often expressed in stroma than in cancer tissue. Moreover, expression of MMP-11 was connected with tumor size and lymph node metastases. Epithelial expression of MMP-11 was mainly expressed in squamous and basaloid carcinomas and was inversely correlated to squamous differentiation.<sup>98</sup> Delebecq et al received similar results – expression of MMP-11 was significantly linked with lymph node metastases.<sup>99</sup>

### MMP-11 in Breast Cancer

The absence of MMP-11 showed alteration of the normal mammary gland on animal model. Histological and immunohistochemical analyses revealed irregularities in structure of ductal tree, and also in alveolar structures. In addition, MMP-11 had an important role in local paracrine

function that stimulate mammary gland branching and epithelial cells proliferation and invading adjacent connective tissue which may promoted tumor progression.<sup>100</sup> Eiro et al elucidated MMP-11 expression by mononuclear inflammatory cells (MICs) in the tumor surrounding stroma as a prognostic marker in BC patients. Expression of MMP-11 by cancer-associated fibroblasts was associated with relapse-free survival and overall survival. However, expression of MMP-11 by MICs was stronger connected with both shortened relapse-free survival and overall survival, thus being better prediction factor for BC patients.<sup>101</sup> Moreover, MMP-11 expressed by MICs had an influence on the cytokine profile and metastatic potential of BC. The lack of expression of MMP-11 by MICs caused the tumor cells released less pro-inflammatory factors. MICs MMP-11+ mainly expressed interleukins or interferon  $\beta$  associated with metastatic spread of cancerous cells.<sup>102</sup> Research of González de Vega et al confirmed that the expression of MMP-11 was elevated in metastatic BC than non-metastatic tumor samples.<sup>103</sup>

## MMP-11 in Prostate Cancer

Increased expression of MMP-11 was connected with poor survival in PCa patients. Immunohistochemistry PCa samples showed expression MMP-11 in the tumor surrounding stroma. Patients with upregulated expression of MMP-11 had shorter survival ratio. High immunoreactivity of MMP-11 was correlated with tumor stage (pT4), poor differentiation in Gleason scale and positive bone metastases. However, no correlation was found with patients age and concentration of prostatic-specific antigen (PSA). It is suspected that high expression of MMP-11 can be used to predict a decrease survival in PCa patients.<sup>104</sup> Roscilli et al collected plasma and tissue samples from patients with PCa. Expression of PCa was strongly marked in cytoplasm of cancer cells. Immunoreactivity in normal prostate glands was slightly visible or negative. Analysis of plasma samples revealed presence of MMP-11. Although, the positive expression of MMP-11 in tumor tissues and serum samples was shown, it is necessary to confirm obtained results in a larger number of patients.<sup>105</sup>

## MMP-11 in Colorectal Cancer

It is believed that expression of MMP-11 can help to predict the presence of metastases and disease progression in patients with CRC. Expression of MMP-11 was detected in tissue of CRC patients, but also in normal colorectal tissue (55.1%; 30.0% respectively). Immunoreactivity of MMP-11

was related to Dukes 'staging, lymph node metastases and distant metastases, but was not related to sex, age and tumor location.<sup>106</sup> Tian et al evaluated MMP-11 mRNA levels using Real-time PCR and MMP-11 expression using immunohistochemistry in fresh tumor samples and healthy colorectal mucosa fragments adjacent to them. In all cases overexpression at mRNA and at protein level was shown in CRC cells in comparison to healthy tissue. Interestingly, this findings are similar to results mentioned before. In this article expression of MMP-11 was also correlated with node metastases, distant metastases and TNM stage.<sup>107</sup> Moreover, Pang et al indicated that elevated serum expression of MMP-11 was correlated with poor prognosis in CRC patients. Serum MMP-11 levels were significantly higher in patients with CRC than in healthy controls. In addition, MMP-11 serum levels were significantly higher in patients with advanced disease status, lymph node metastases, distant metastases and higher grade in TNM scale. Additionally, high concentrations of MMP-11 were identified as an independent prognostic factor for 5-year mortality.<sup>108</sup>

## Summarizing

Increased expression of MMP-11 has been noticed in all types of cancers described below. High expression of MMP-11 was observed more often in stromal cells surrounding NSCLC tissue than in cancer cells themselves. Literature analysis also allowed the conclusion that MMP-11 expression may be associated with the presence of lymph node metastases in NSCLC. Interestingly, a similar trend was observed in CRC patients. Additionally, in CRC patients was observed correlation between expression of MMP-11 and distant metastases and TNM stage. In BC higher expression in MICs may be a prognostic marker. Moreover, expression of MMP-11 by MICs promoted metastatic potential of BC. Similarly, expression of MMP-11 in PCa patients was correlated with distant metastases and also with tumor stage and poor survival ratio.

## Conclusions

Matrilysins and stromelysins are a family of enzymes with broad substrate specificity with the capacity to degrade the components of the ECM, but also non-matrix components. They are responsible for maintain the homeostasis of ECM and physiological functions of cells. Disturbances in expression and activation of matrilysins and stromelysins often results in the development of inflammation and in consequence dysplastic changes in cells, and even cancer transformation. Our research



team over the last years carefully investigated various MMPs in gynaecologic malignancies, e.g., ovarian cancer,<sup>109,110</sup> cervical cancer<sup>111,112</sup> and BC.<sup>113,114</sup> Our data, indicated that MMPs had a diagnostic utility in gynaecologic cancers, also a wide scientific literature seems to confirmed this reports. Moreover, in other malignancies, exist also a broad spectrum of research proved statistical significance between tissue expression or plasma/serum levels of MMPs and cancer development. As we can see, the literature cited in this article indicated matrilysins and stromelysins in various types of cancers. These enzymes are involved in development, metastases and angiogenesis thus affect prognosis and survival of patients. However, data are still unclear and sometimes gives us contradictory information. Thus it is essential to elucidate the exact role of these enzymes in pathological processes, especially in cancerogenesis.

## Disclosure

The authors declare no conflicts of interest.

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