Published in final edited form as:

J Control Release. 2017 August 10; 259: 62–75. doi:10.1016/j.jconrel.2017.01.034.

Matrix-metalloproteinases as targets for controlled delivery in cancer: an analysis of upregulation and expression

Kyle J. Isaacson^{a,c}, M. Martin Jensen^{a,c}, Nithya B. Subrahmanyam^{b,c}, and Hamidreza Ghandehari^{a,b,c}

^aDepartment of Bioengineering, University of Utah, Salt Lake City, UT, USA

^bDepartment of Pharmaceutics and Pharmaceutical Chemistry, University of Utah, Salt Lake City, UT, USA

^cUtah Center for Nanomedicine, Nano Institute of Utah, University of Utah, Salt Lake City, UT, USA

Abstract

While commonly known for degradation of the extracellular matrix, matrix metalloproteinases (MMPs) exhibit broad potential for use in targeting of bioactive and imaging agents in cancer treatment. MMPs are upregulated at all stages of expression in cancers. A comprehensive analysis of published literature on expression of all MMP subtypes at the genetic, protein, and activity levels in normal and diseased tissues indicate targeting applicability in a variety of cancers. This expression significantly increases at advanced cancer stages, providing an improved opportunity for controlled release in higher-stage patients. Since MMPs are integral at every stage of metastasis, MMP roles in cancer are discussed with a focus on MMP distribution and mobility within cells and tumors for cancer targeting applications. Several strategies for MMP utilization in targeting – such as matrix degradation, MMP cleavage, MMP binding, and MMP-induced environmental changes – are addressed.

Graphical abstract

Keywords

Matrix metalloproteinases; drug targeting; controlled release; upregulation; expression; cancer

Corresponding Author Information: Hamidreza Ghandehari, hamid.ghandehari@utah.edu, University of Utah, 36 S Wasatch Dr., Salt Lake City, UT 84112.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

INTRODUCTION

Adverse effects prevalently accompany cancer chemotherapy. To reduce these adverse effects and improve patient quality of life, it is imperative that advancements to current treatments be made. Development of novel systems to target, localize, and prolong residence time of bioactive compounds within cancerous tissues has the potential to minimize deleterious off-target effects in healthy tissue. To achieve enhanced exposure of cancer tissue to drug, drug delivery systems (DDSs) can be designed to respond to the tumor and metastatic microenvironments for localized action. The cancer microenvironment often differs from healthy tissue via extracellular matrix (ECM)-degradation protein concentrations[1]. As a subclass of ECM-degradation proteins with large concentration differences between healthy and cancer tissues, matrix-metalloproteinases (MMPs) yield themselves as opportune candidates for localized delivery.

What are MMPs?

MMPs are calcium-dependent endopeptidases that utilize three amino acids as ligands for zinc ion coordination to achieve their catalytic action. To date, 23 MMPs have been discovered in humans (MMP-23A and MMP-23B are considered as one protein in this review, as they are identical proteins encoded by a duplicated gene[2]). The various MMPs each recognize and cleave specific peptide sequences commonly found in a variety of ECMs and other components[3], with the most typical substrates being many collagen types[4–6], gelatin[7], aggrecan[8], laminin[9], elastin[6,10], fibronectin[11,12], fibrinogen[13], and fibrin[14]. Substrate specificities and amino acid sequences have led to classification of MMPs into various categories, i.e., the collagenases (MMP-1, MMP-8, MMP-13), the gelatinases (MMP-2, MMP-9), the stromelysins (MMP-3, MMP-10, MMP-11), the matrilysins (MMP-7, MMP-26), and membrane-type (MMP-14, MMP-15, MMP-16, MMP-17, MMP-24 MMP-25)[15]. Seven other MMPs are not classified into substrate-dependent groups, with many of their corresponding substrates dependent upon the tissue or cells in which these MMP subtypes are mainly expressed (MMP-12: macrophages[16]; MMP-19: placenta, lung, pancreas, ovary, spleen, intestine[17]; MMP-20: enamel[18]; MMP-21: ubiquitous within tissues[19]; MMP-23: reproductive tissues[20]; MMP-27: ubiquitous in all tissues except brain[19]; and MMP-28: testis, keratinocytes[21])[22]. The specific substrates of the various MMPs are summarized in the reviews by Visse and Nagase[22,23].

All MMPs are synthesized in an inactive proenzyme state in which the zinc-containing catalytic domain interacts with a cysteine residue[24,25]. Disruption of this zinc-cysteine interaction via activation factors partially activates the enzyme and promotes the autocatalysis of the propeptide region, rendering the MMP fully active[26,27]. Membrane-type MMPs and the secreted furin-activated MMPs (MMP-11, MMP-21, MMP-28) are known to undergo activation intracellularly, followed by either immediate lipid membrane localization or extracellular secretion, respectively[23,28–34]. Other secreted MMPs are activated extracellularly via various mechanisms[35–37]. MMP-2 is commonly activated from its proenzyme state at the cell surface by forming a complex with an activated membrane-associated MMP[38]. In the laboratory, mercurial compounds can be utilized to

induce activation[39]. MMP activation is a highly regulated step, dependent on MMP type, but generally influenced by soluble factors, ECM-cell interactions, and cell-cell interactions[40]. Inhibitors, such as tissue inhibitors of metalloproteases (TIMPs), serve to reduce activity of activated MMPs; however, latent gelatinases can form complexes with TIMPs to promote MMP-2 activation or for other unknown functions[41,42].

MMPs are generally either excreted into the extracellular environment or remain membrane-bound; however intracellular MMP concentrations are often present. When in the intracellular environment, most MMPs remain preserved in a latent proenzyme state[43], yet activated forms and even novel isoforms have been identified intracellularly[28,44,45].

Biological Function of MMPs

Classically, MMPs are known as ECM degradation enzymes, ultimately having effects on ECM dynamics and fundamental cell behavior – proliferation[46], adhesion[47], migration[48], differentiation[49], and apoptosis[50]. While each subtype targets specific substrates, MMPs recognize and cleave specific peptide sequences of the various ECM protein components. The three-dimensional structure of ECM components affects the cleavage capability of individual MMP subtypes[51], despite MMP catalytic domain polypeptide folding being only slightly altered among subtypes[16]. The important roles of MMPs in ECM remodeling provide broad potential impacts in the immediate external cellular environment.

However, MMP biological function is not limited to the ECM. Interestingly, approximately only 20% of MMP substrates are ECM molecules and regulators[52]. Other MMP substrates include receptors[53], growth factor binding proteins[54], and cytokines[55]. In fact, neither MMP-11 nor MMP-23 have any known ECM substrates, exhibiting only very weak ECM activity[22,23,56,57]. This pleiotropy leads to a myriad of effects in enzyme activation[58], cell signaling regulation[59], chemokine processing[60], and membrane shedding[61], with ultimately larger-scale impacts in embryogenesis and embryo development[62], tissue morphogenesis[63], tissue homeostasis[64], wound healing[65], and inflammation[53]. As expected with the wide range of effects, MMP dyshomeostasis has been associated with several diseases, including arthritis[66], cardiovascular diseases[67], pulmonary diseases[68], and cancer[69]. The biological function of MMPs is addressed more extensively in external reviews by Vu, Löffek, and Rodríguez[70–72].

Targeting of MMPs

As degradation enzymes with promiscuous substrate specificity, MMPs provide an avenue for localized controlled release of anticancer drugs at or near tumor tissues. To highlight the potential advantages of MMPs as cancer targets, this review will address MMP upregulation and overexpression in cancer, role in metastatic disease, and distribution and motility in and around cancer environments. Furthermore, a brief evaluation of current utilization of MMPs as targets will be discussed. In summary, this mini-review will focus on the use of MMPs as targets for localization and controlled release of bioactive agents in the treatment of cancer. Design and development of drugs for MMP inhibition has been thoroughly discussed in other reviews[15,73–75].

MATRIX METALLOPROTEINASES IN CANCER: WHY ARE THEY WORTHWHILE TARGETS?

Regulation and Expression

MMPs are regulated at many levels[76]: (1) RNA transcription, (2) protein synthesis, (3) secretion and intracellular trafficking, (4) subcellular or extracellular localization (compartmentalization), (5) zymogen activation, (6) endogenous protease inhibitor expression levels, and (7) MMP degradation (inactivation). Upregulation of at least one MMP subtype has been observed for all of these regulatory stages in at least one form of cancer[77–83].

To comprehensively evaluate MMP upregulation in cancerous tissues, a database categorizing 70 peer-reviewed journal articles was created for this review, in which the genetic, protein, and activity levels were distinguished. Of the articles included in the database, methods utilized for upregulation quantification included: immunohistochemistry, qPCR, microarray analysis, Western blotting, ELISA, substrate zymography, and fluorogenic MMP substrates. Despite having discovered MMP upregulation in a variety of fluids (pleural effusion fluid[84], serum[85], plasma[86], ascitic fluid[87], sputum[88], pancreatic juices[89], urine[90], fecal material[91], bronchoalveolar lavage fluid[92], nipple aspirate fluids[93], and cerebrospinal fluid[94]), only literature evaluating normal and diseased human tissues was included in the database. Serum and plasma MMP concentrations were not included as upregulated cancer patient serum concentrations are often an order of magnitude lower than tissues obtained from healthy patients[85,95]. The analysis weighted studies by number of patients in order to reduce the impact of outlier tissue samples. Complete database methods (including limitations to the analysis) are available in supplemental information (Methods S1). Database results showing upregulation levels in many forms of cancer for the most studied MMPs (MMP-1 through MMP-9) are shown in Table 1, and less-studied MMPs (MMP-10 through MMP-28) are included in Table S1. In Table 1 and Table S1, healthy and cancer tissue expression refers to the percentage of tissue samples deemed to have sufficient MMP subtype expression by immunohistochemistry to be considered positive for the expression of the MMP by the authors of the individual studies.

While whether all or only specific MMP subtypes exhibit upregulation remains disputed, several MMPs show greater than 10-fold average genetic, protein, and/or activity expression increases (Table 1). Furthermore, the level of upregulation positively correlates with cancer stage, as illustrated in Figure 1 (data obtained from the compiled database), which represents an analysis comparing the patient tissue immunohistochemical expression, genetic expression, protein expression, and activity levels of all MMP subtypes in all cancer types against patient population cancer stage (see Methods S2 for complete methods and limitations of analysis). While only the genetic and protein expression correlated to statistical significance ($p=0.007$, $p=0.017$, respectively), expression levels in all evaluated cases were shown to positively correlate with increasing cancer stages. Few individual MMP subtypes showed a statistically-significant correlation to cancer stage via this analysis (data not shown), yet those that did are listed here: MMP-1 (Protein: $p=0.014$), MMP-8 (Protein:

$p < 0.001$), MMP-10 (Percent: $p = 0.044$, Protein: $p = 0.003$), MMP-14 (Genetic: $p = 0.046$), MMP-28 (Percent: $p = 0.015$, Protein: $p < 0.001$).

The consequences of MMP upregulation are grave, as increased MMP subtype expression has been correlated with increased angiogenesis[96], cell proliferation[46], and cell migration[97], and shown to decrease cancer cell sensitivity to natural killer cells[98]. MMP upregulation is further associated with increased regional lymph node[99] and brain metastases[100], higher TNM stage[101], poorer patient survival[102], greater tumor invasion depth[103], poorer tumor differentiation[104], greater likelihood of recurrence[105], and poorer prognosis[106]. However, as their concentrations are increased in both primary and metastatic tumors, MMPs make strong candidates as targets for systemic delivery for controlled release of chemotherapeutics, unlike many biomarkers that show significant differences in expression between primary and metastatic tumors[107–110]. Furthermore, the lower MMP expression within the bloodstream compared to both healthy and tumor tissues can reduce intra-vessel drug release from properly-engineered systemic delivery vehicles during transport [further discussed below in MMP-Cleavage from Nanocarriers].

Role in Metastasis

Metastasis is the predominant cause of mortality for most solid tumor cancer[111], and MMPs play a multi-layered and pivotal role in metastasis[111,112]. Evidence supports both pro-metastatic and anti-metastatic roles of MMPs[113], yet MMPs are known to be involved in every stage of metastasis formation[113–115]. MMP-7 converts E-cadherin, a cell-cell adhesion protein, into a soluble form in cancer, allowing cancer cells to dislodge from the bulk tumor and become motile[116]. As MMPs degrade the surrounding ECM components (including the basement membrane), a migratory pathway is created through which local invasion of tumor cells is facilitated[117–119]. Cleavage of fibrous ECM proteins exposes normally hidden sites and epitopes which can have biological activity that promote growth[119]. Increased MMP activity also alters the structural tension in the matrix, altering mechanotransductive forces and leading to changes in cell-matrix signaling cues[120]. The release of ECM-bound signaling molecules that are normally only exposed to the cell surface in a tightly-regulated manner often accompanies increased MMP activity and ECM fragmentation, which can further promote proliferation and mobility[121]. MMP activity also instigates cytokine and growth factor expression, conducive to angiogenesis, tumor growth, and metastasis[113].

MMP roles in metastasis are not confined to only the localized ECM. Tumor cell intravasation into the circulation has been shown to be supported via MMP-1 regulation of endothelial permeability and transendothelial migration[122]. Furthermore, MMPs are directly involved in capillary wall adhesion after circulatory transport due to removal of endothelial cell adhesion molecules and formation of invadopodia, potentially playing a role in localization of metastases[114,115,123–125]. After metastatic cell entrance into tissues, membrane-associated MMPs facilitate adhesion to the regional ECM via CD44-shedding[126]. MMP-facilitated proteolysis of the ECM then allows for metastatic cell motility and settling into the new tissue, to begin the formation of a secondary tumor[127].

As MMPs are involved in the core metastatic functions of cancer cells, drug delivery mechanisms that target MMPs can essentially target cancer cells during all stages of metastasis.

Cellular Distribution and Mobility

While it may seem that membrane-bound and secreted MMPs have designated distribution, large MMP localization changes occur within cancer cells. Most intracellular MMPs reside in a zymogen state, yet besides proMMP-26, few MMP proenzymes are stored within the cells, as they are compartmentalized for membrane association or rapid secretion[128]. Interestingly, MMP-2 shows intracellular activity in nearly all healthy tissues[129], but is often associated with apoptosis in healthy tissues[130]. Tumor cells show even higher intracellular gelatinolytic activity (likely from MMP-2) particularly at the invasive tumor front, yet apoptosis is not induced[131]. Like MMP-2, MMP-3 shows intracellular activity being highly associated with apoptosis, except in cancer[132–134]. MMP-1, MMP-7, MMP-8, and MMP-9 are also rarely activated intracellularly in healthy cells during times of cellular stress[135], but reliable cancer-related intracellular activity studies regarding these MMPs are scarce. Evidence for intracellular activity has also been found for MMP-11, MMP-27, and the four Type-1 membrane-type MMPs via a normal furin activation mechanism, but these active MMPs seem to be rapidly transported to the membrane[33,136]. One very interesting finding is that MMP-9 is known to permanently associate within the membrane of cancer cells – but not healthy cells – via unknown mechanisms[137], yet only stromal-associated, not membrane-anchored, MMP-9 have been shown to affect growth and angiogenesis[138]. MMP mobility and compartmentalization within cells is known to be affected by interactions with many intracellular components (reviewed by Mannello[139]), including through complex formation with natural inhibitors (MMP-9)[140].

Tumor Distribution and Mobility

While MMP distribution throughout the tumor varies among cancer types, a few general trends can be claimed. MMP-2 shows greatest abundance at the invasive front, while the highest expression of MMP-7 and MMP-14 is found in the tumor center[141,142]. MMP-9 is most abundantly found at the periphery in primary tumors, but within the tumor core in metastases[143,144]. The invasive front shows the highest expression of MMP-11[142,145]. The most prevalent tumor distribution of commonly studied active MMPs is illustratively represented in Figure 2, using data from the following studies [141–154]. Tumors exhibit the greatest metastatic activity when MMP expression is highest in all regions of the tumor (when MMP/TIMP ratio is highest in both tumor center and invasive front)[142]. MMPs, in general, can be found with high expression in many tumor surrounding cells, such as ECM cells, immune cells, fibroblasts, and endothelial cells[155]. This broad expression provides plenty of opportunities to use MMP-targeting techniques for the localization of therapeutic compounds within the immediate cancer cell vicinity. Due to the large variation in MMP subtype distributions, special consideration must be taken in electing a particular subtype as a drug delivery target. Nevertheless, one cannot ignore that secreted MMPs are highly mobile, showing substantial diffusion even within the ECM environment that can cause changes in subtype tumor localization[156].

STRATEGIES FOR TARGETING

MMP-based targeting strategies are rapidly diversifying (Figure 3). While many drug delivery systems rely on delivery of already active drugs, MMP-targeted systems often deliver MMP-activatable prodrugs, covered in external reviews[157,158].

Matrix Degradation

The enzymatic activity of MMPs can be leveraged to create release depots that dynamically respond to their environment[159]. Hydrogels are comprised of soluble polymers cross-linked together via chemical or hydrogen bonds, electrostatic attraction, or van der Waals interactions. By incorporating sequences in the polymeric network – most frequently peptides – that are cleavable by MMPs, cleavage of polymer backbones, side chains, and/or crosslinks can be designed to occur within tumor microenvironments. This cleavage results in swelling and eventual degradation of the gel, which can be utilized to accelerate the release of bioactive molecules from the matrix[160]. These strategies have been extensively explored within the field of tissue engineering, but to a far lesser extent in drug delivery. Two strategies exist for implantation of macroscale matrices into cancerous tissue: first, surgical implantation either through direct placement or depositing the material in the void following tumor resection; second, injection of an *in situ* gelling solution from a needle or catheter.

MMP-responsive silk-elastinlike protein polymers (SELPs) have been investigated for the delivery of adenoviruses to head and neck squamous cell carcinoma and other bioactive compounds from an *in situ* gelling matrix[161–164]. SELPs are constructed using recombinant genetic techniques to combine the strength of silk and the biocompatibility and thermoresponsive solubility of elastin with exquisite control over sequence, silk:elastin ratio, and molecular weight[165–167]. An injectable *in situ* gelling SELP polymer construct, SELP 815K (which contains 6 repeats of 8 silklike GAGAGS units, 15 elastinlike GVGVP units, and one lysine-substituted elastinlike GKGVP unit), with MMP-responsive sequence inserted into the elastin block, at the boundary between silk and elastin blocks, and within the silk blocks, undergoes a thermal liquid-to-solid transition between room and body temperature[160,168]. Location of the MMP-responsive sequence affected gel mechanical properties, the degree of responsiveness, and survival outcome in animals[161,168–170]. When the MMP-responsive sequences are incorporated into the elastin backbone or flanking regions, mechanical properties are preserved; however, insertion of the sequences into the silklike units, responsible for crosslinking within SELP gels, drastically decreased the mechanical rigidity and accelerated release of virus and degradation *in vivo*. MMP-directed release of viral gene therapy from MMP-responsive SELP hydrogels was shown to improve survival over non-responsive SELP gels and intratumoral injection of virus[170].

Implantable hydrogel-based devices have been created to selectively deliver therapies that respond to the degree of MMP activity in the local environment. These hydrogels are designed to be inserted into the post-resection cavity of glioblastoma multiforme (GBM) patients to prevent relapse from residual cancer cells[159]. Poly(ethylene glycol) (PEG)-based hydrogels were created with cisplatin attached pendently via MMP-2 cleavable peptides (GPLGVRC) and shown to only release therapeutics in the presence of

MMP-2[171–174]. The rate of degradation was primarily influenced by the ability of MMPs to penetrate into the matrix and enzymatic kinetics, rather than drug diffusivity[174]. Several other polymers could be potentially utilized in the future development of these systems.

In designing MMP-responsive matrices, one must consider base therapeutic release levels, polymer concentration, number of MMP-degradable sequences per polymer, and location of MMP-responsive sequences within the gel structure. A key design parameter to consider for this type of construct is the correlation between polymer density, porosity, and release, as release rates will not be dependent upon MMP activity for readily diffusible therapeutics. One method to overcome this obstacle is the tethering of freely-diffusing compounds to the matrix with degradable linkers in many particle-based systems [see MMP-Cleavage from Nanocarriers]. Pore size must be sufficient to allow MMPs access to cleavage sites. The polymer concentration within the gels will also impact release profiles, with lower polymer concentration increasing responsiveness of the constructs to MMP-induced release[170].

MMP-Cleavage from Nanocarriers

Anticancer drugs may be attached to nanocarriers via MMP-cleavable linkers. These peptide linker sequences can be tailored for particular MMP subtypes and have been shown to significantly enhance drug release when compared to a scrambled peptide linker[175]. Several different MMP-sensitive nanocarriers have been developed, including natural polymer-drug conjugates[176,177], synthetic polymer-drug conjugates[178], micelles[179], liposomes incorporating tailored lipopeptides[180], nanovesicles[181], and self-assembling peptide fragments[182]. These systems have been used for delivery of chemotherapeutics[183], prodrugs[184], and siRNA for gene therapy[185]. Many anticancer drugs have been developed using solely MMP-cleavable linkers for activation of prodrugs, viruses for gene therapy[186], or toxins[187,188] without the use of a nanocarrier. Recently, alterations have been made that combine matrix degradation with systemic delivery by incorporating the cleavage sites directly within the nanocarrier main structure, instead of linkers between pendant groups[189–191].

These novel approaches increase tumor penetration depth of the free drug due to the shrinking of the particle conditional upon degradation, as evidenced by a dendrimer-based gelatin matrix nanoparticle DDS[192]. Theranostic approaches are now being developed, as shown by Ansari et al with a MMP-14-cleavable linker to activate a prodrug while simultaneously initiating fluorescence. However, it must be noted that the utilized cell line abnormally overexpressed MMP-14 (over 1000-fold) when compared to other cancer cell lines[193]. Level of targeted MMP overexpression was determined to be highly significant for therapeutic efficacy of MMP-cleavable nanocarriers in a separate study that compared *in vivo* efficacy against cancer cell lines with differing MMP expression for tumor models[178]. Unfortunately, the majority of these systems have only been evaluated against primary tumors, and very limited studies regarding metastatic localization and release are available. One recent study utilizing a MMP-cleavable linker to a photosensitizer for photodynamic therapy provides promising evidence in destruction of bone metastases *in vivo*[194].

As active MMPs are known to circulate in the bloodstream[195], MMP-cleavable nanocarriers risk premature systemic release of free drug. However, MMP concentrations within the bloodstream of cancer patients have been shown to be approximately 10-fold or more lower than even the healthy tissues of those same cancer patients[85,95], indicating that bloodstream MMP activity should be a concern for off-target drug release dependent upon circulation time. Moreover, ideal nanocarriers would be designed to release their drug cargo above a certain MMP concentration threshold in order to reduce systemic free drug concentrations and minimize release within healthy tissues. A concentration threshold-dependent release of drug from nanocarriers could allow for sufficient time for clearance from healthy tissues and decrease side effects.

MMP-Targeting via Ligand Binding

Increased expression of MMPs in solid tumors and metastases makes them attractive for targeting by binding antibodies or peptides[69]. In traditional ligand-based targeting, a binding element is attached to a therapeutic carrier. When the binding ligand contacts its target, the carrier is trapped and elevates the local therapeutic concentration. Once such targeting peptide is cyclic peptide inhibitor (CTT), CTTHWGFTLC, which binds specifically as an inhibitor to the gelatinases, MMP-2 and MMP-9. CTT has been used to enhance the delivery of liposomes and protein nanocages compared to non-targeted vessels *in vivo* in murine cancer models[196–199]. Given the peptidic nature of CTT, it can also be seamlessly grafted onto biologics to enhance their accumulation in rapidly growing tumors[200]. As part of a triple fusion protein, CTT was combined with endostatin mimic and kringle 5 (AARP), which are recombinant versions of endogenous antiangiogenic agents. Testing in a syngeneic mouse model with Lewis lung cancer cell line (LL/2) showed that the fusion peptide with CTT was more effective at retarding tumor growth than clinical endostatin. *In vitro* and histological testing showed AARP more effective in suppressing endothelial cell activation (proliferation, migration, and tube activation)[201]. MMP-targeting peptides can be used to enhance localization into tumors and increase the efficacy of therapeutic cargo. A key challenge for MMP targeting is the existence of many counter-targets, proteins that are homologous to the target but have no significant role in the disease, and anti-targets, proteins with essential functions whose down-modulation results in clinically unacceptable side effects[2].

MMP-binding peptides and anti-MMP antibodies have been investigated for the purpose of drug delivery to only a very limited extent[159,202]; however, targeting individual MMP subtypes could potentially lead to drug localization at particular sites along the cancer cell membrane or within a broader tumor region. Several peptides utilized by MMP inhibitors bind to many MMP subtypes[203,204], yet the majority of these inhibitors have shown mediocre efficacy in clinical trials[73]. While MMP subtype-specific inhibitors are now recommended for MMP inhibition[205], use of broad-spectrum MMP-specific peptide sequences in MMP-binding drug delivery systems could potentially bypass limitations of specific MMP subtype targeting[206]. Furthermore, an entire MMP inhibitor (not just a peptide) was investigated as a MMP-imaging theranostic when radiolabeled TIMP-2 was designed for Kaposi sarcoma[207]. In a study of five human patients, however, the tracer was shown to predominantly distribute to the kidneys with no distinguishable signal in other

tissues, casting doubt on TIMP effectiveness for localization of drugs to tumors[208]. Several labs have combined targeting elements for other targets, such as CD44[209] or HER2[210], with MMP-cleavable linkers that function as secondary selection factor to trigger drug release or activate cell penetrating peptides after tumor accumulation[199,211,212]. However, as these particles used MMP-cleavable linkers rather than binding peptides, they are considered to use MMP-cleavage as their mode of targeting for the purpose of this review [See MMP-Cleavage from Nanocarriers].

Targeting MMP-Induced Environmental Effects

The increased MMP activity leads to an altered tumor microenvironment, which in itself can provide opportunities for targeting strategies. Some of these changes include increased degradation of proteins and ECM components, such as collagen, laminin, and proteoglycans. A few examples of potential tumor microenvironment targets altered by MMP upregulation include increased fibronectin levels[213], amplified concentrations of lysyl oxidase (LOX) [214], the increased expression of MMP inhibitors[215], the denaturation of collagen in localized cancer ECMs[216], and greater CD44 cleavage. A fibronectin-targeting peptide attached to an MRI contrast agent effectively detected micrometastases and could easily be utilized for therapeutic delivery[217]. A peptide sequence with favorable kinetic properties for LOX-mediated peptidyl lysine oxidation has also been utilized for targeting of LOX environments[218]. While the majority of targeting of TIMPs has been directed toward gene regulation for MMP inhibition, TIMPs are non-intuitively upregulated alongside MMPs in cancers, likely due to their complexation with gelatinases having MMP activation functionality and their cell proliferation stimulation. Anti-TIMP-1 monoclonal antibodies have been shown to effectively localize in neoplastic tissues and provide an opportunity for drug targeting[219]. Collagen-mimetic peptides (CMPs) are shown to preferentially bind to denatured collagen via a triple helical peptide assembly and provide one of the most intriguing avenues for targeting MMP-induced effects in cancer drug delivery[220,221] (see Figure 3). Cleaved CD44 is known to be targeted by hyaluronic acid and has been investigated for drug delivery applications with promising results in the circumvention of chemoresistance[222]. One could contest that these mechanisms are essentially targeting other ECM components besides MMPs, yet we felt that MMP-induced environmental effects merited consideration as a targeting method to allow comprehensive evaluation.

Enhancing MMP Upregulation

MMPs are upregulated via a variety of mechanisms, several of which involve external stimuli. While external triggering of local overexpression of MMPs to enhance efficacy of drug delivery has scarcely been investigated, this approach merits discussion in MMP-responsive cancer drug delivery. External upregulation of MMPs could likely advance cancer progression; however, the added efficacy of a highly potent compound released in concentrated MMP environments could be worth pursuing. Higher levels of targeted MMP expression when tested with MMP-responsive nanocarriers have been correlated with quicker degradation and release kinetics[160], increased dose administration[178], and reduced tumor volume[178]. With further investigation, one may find an enhancement of localization, lessening of off-target side effects, and improvements in overall survival.

Mild hyperthermia (39°C for 240 minutes) has been shown to upregulate MMP-2 and MMP-9 protein concentrations by 147% and 78%, respectively[223], likely caused by heat shock protein upregulation[37]. Further methods to externally increase MMP activity include mechanical induction to replicate a more rigid ECM[224], injection of MMP regulators[225], gene delivery[226], or oxidative stress[227]. Curiously, mechanical induction of MMP overexpression in MDA-MB-231 cells was correlated with advanced resistance to free drug chemotherapeutics, but was not tested against MMP-induced controlled release systems[224]. This enhanced chemoresistance has been observed in various other studies evaluating high expression of MMPs (not externally induced) as well[228–232]. Clearly, enhancing efficacy of MMP-responsive drug carriers via external MMP upregulation merits further investigation.

CONCLUSION AND FUTURE DIRECTIONS

Overexpression and corporeal distribution in cancers qualify MMPs as a target for use in engineering drug delivery systems for controlled release. Due to the strong variability among MMP subtypes, further analysis is needed to define specific subtype expression profiles with individual cancers. Initial MMP-sensitive drug delivery systems have yielded substantial promise in improving localized pharmacological effect while limiting off-target effects in cancer. While a comprehensive evaluation of the efficacy of MMP-sensitive drug delivery systems on metastases has yet to be performed, novel methods utilizing MMP proteolytic activity for cancer-responsive drug delivery are likely to be developed. Externally enhancing MMP expression in localized regions could prove beneficial in supplementing MMP-targeted systems achieve much-needed efficacy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The authors thank Marcelo Correa for aiding in the technical design of Figures.

FUNDING SOURCES

This work was supported by the National Institutes of Health [R01CA107621, R42CA168123]; fellowships from the University of Utah [Campbell Endowed Graduate Fellowship and Nanotechnology Training Program (KJI)]; and a National Science Foundation Graduate Research Fellowship [1256065 (MMJ)].

References

1. Lu P, Weaver VM, Werb Z. The extracellular matrix: A dynamic niche in cancer progression. *J Cell Biol.* 2012; 196:395–406. DOI: 10.1083/jcb.201102147 [PubMed: 22351925]
2. Overall CM, Kleinfeld O. Tumour microenvironment - opinion: validating matrix metalloproteinases as drug targets and anti-targets for cancer therapy. *Nat Rev Cancer.* 2006; 6:227–239. DOI: 10.1038/nrc1821 [PubMed: 16498445]
3. Turk BE, Huang LL, Piro ET, Cantley LC. Determination of protease cleavage site motifs using mixture-based oriented peptide libraries. *Nat Biotechnol.* 2001; 19:661–667. DOI: 10.1038/90273 [PubMed: 11433279]

4. Lauer-Fields JL, Juska D, Fields GB. Matrix metalloproteinases and collagen catabolism. *Biopolym - Pept Sci Sect.* 2002; 66:19–32. DOI: 10.1002/bip.10201
5. Ottl J, Gabriel D, Murphy G, Knäuper V, Tominaga Y, Nagase H, Kröger M, Tschesche H, Bode W, Moroder L. Recognition and catabolism of synthetic heterotrimeric collagen peptides by matrix metalloproteinases. *Chem Biol.* 2000; 7:119–132. DOI: 10.1016/S1074-5521(00)00077-6 [PubMed: 10662694]
6. Van Doren SR. Matrix metalloproteinase interactions with collagen and elastin. *Matrix Biol.* 2015; 44–46:224–231. DOI: 10.1016/j.matbio.2015.01.005
7. Atkinson SJ, Ward RV, Reynolds JJ, Murphy G. Cell-Mediated Degradation of Type-IV Collagen and Gelatin Films Is Dependent on the Activation of Matrix Metalloproteinases. *Biochem J.* 1992; 288:605–611. [PubMed: 1463464]
8. Chambers MG, Cox L, Chong L, Suri N, Cover P, Bayliss MT, Mason RM. Matrix metalloproteinases and aggrecanases cleave aggrecan in different zones of normal cartilage but colocalize in the development of osteoarthritic lesions in STR/ort mice. *Arthritis Rheum.* 2001; 44:1455–1465. DOI: 10.1002/1529-0131(200106)44:6<1455::AID-ART241>3.0.CO;2-J [PubMed: 11407708]
9. Bair EL, Chen ML, McDaniel K, Sekiguchi K, Cress AE, Nagle RB, Bowden GT. Membrane type 1 matrix metalloprotease cleaves laminin-10 and promotes prostate cancer cell migration. *Neoplasia.* 2005; 7:380–9. DOI: 10.1593/neo.04619 [PubMed: 15967115]
10. Mecham RP, Broekelmann TJ, Fliszar CJ, Shapiro SD, Welgus HG, Senior RM. Elastin Degradation by Matrix Metalloproteinases. *J Biol Chem.* 1997; 272:18071–18076. DOI: 10.1074/jbc.272.29.18071 [PubMed: 9218437]
11. Steffensen B, Chen Z, Pal S, Mikhailova M, Su J, Wang Y, Xu X. Fragmentation of fibronectin by inherent autolytic and matrix metalloproteinase activities. *Matrix Biol.* 2012; 30:34–42. DOI: 10.1016/j.matbio.2010.09.004.Fragmentation
12. Hsu CC, Lai SC. Matrix metalloproteinase-2, -9 and -13 are involved in fibronectin degradation of rat lung granulomatous fibrosis caused by *Angiostrongylus cantonensis*. *Int J Exp Pathol.* 2007; 88:437–443. DOI: 10.1111/j.1365-2613.2007.00554.x [PubMed: 18039280]
13. Hiller O, Lichte A, Oberpichler A, Kocourek A, Tschesche H. Matrix metalloproteinases collagenase-2, macrophage elastase, collagenase-3, and membrane type 1-matrix metalloproteinase impair clotting by degradation of fibrinogen and factor XII. *J Biol Chem.* 2000; 275:33008–33013. DOI: 10.1074/jbc.M001836200 [PubMed: 10930399]
14. Bini A, Itoh Y, Kudryk BJ, Nagase H. Degradation of cross-linked fibrin by matrix metalloproteinase 3 (stromelysin 1): Hydrolysis of the ?? Gly 404-Ala 405 peptide bond. *Biochemistry.* 1996; 35:13056–13063. DOI: 10.1021/bi960730c [PubMed: 8855941]
15. Cathcart J, Pulkoski-Gross A, Cao J. Targeting matrix metalloproteinases in cancer: Bringing new life to old ideas. *Genes Dis.* 2015; 2:26–34. DOI: 10.1016/j.gendis.2014.12.002 [PubMed: 26097889]
16. Shapiro SD, Kobayashi DK, Ley TJ. Cloning and characterization of a unique elastolytic metalloproteinase produced by human alveolar macrophages. *J Biol Chem.* 1993; 268:23824–23829. <http://www.ncbi.nlm.nih.gov/pubmed/8226919>. [PubMed: 8226919]
17. Pendas AM, Knauper V, Puente XS, Llano E, Mattei M-G, Apte S, Murphy G, Lopez-Otin C. Identification and Characterization of a Novel Human Matrix Metalloproteinase with Unique Structural Characteristics, Chromosomal Location, and Tissue Distribution. *J Biol Chem.* 1997; 272:4281–4286. DOI: 10.1074/jbc.272.7.4281 [PubMed: 9020145]
18. Llano E, Pendas AM, Knauper V, Sorsa T, Salo T, Salido E, Murphy G, Simmer JP, Bartlett JD, Lopez-Otin C. Identification and structural and functional characterization of human enamelysin (MMP-20). *Biochemistry.* 1997; 36:15101–15108. [pii]. DOI: 10.1021/bi972120y [PubMed: 9398237]
19. Nuttall RK, Sampieri CL, Pennington CJ, Gill SE, Schultz GA, Edwards DR. Expression analysis of the entire MMP and TIMP gene families during mouse tissue development. *FEBS Lett.* 2004; 563:129–134. DOI: 10.1016/S0014-5793(04)00281-9 [PubMed: 15063736]
20. Velasco G, Pendás AM, Fueyo A, Knäuper V, Murphy G, López-Otín C. Cloning and characterization of human MMP-23, a new matrix metalloproteinase predominantly expressed in

- reproductive tissues and lacking conserved domains in other family members. *J Biol Chem.* 1999; 274:4570–4576. DOI: 10.1074/jbc.274.8.4570 [PubMed: 9988691]
21. Lohi J, Wilson CL, Roby JD, Parks WC. Epilysin, a Novel Human Matrix Metalloproteinase (MMP-28) Expressed in Testis and Keratinocytes and in Response to Injury. *J Biol Chem.* 2001; 276:10134–10144. DOI: 10.1074/jbc.M001599200 [PubMed: 11121398]
 22. Visse R, Nagase H. Matrix metalloproteinases and tissue inhibitors of metalloproteinases: structure, function, and biochemistry. *Circ Res.* 2003; 92:827–839. DOI: 10.1161/01.RES.0000070112.80711.3D [PubMed: 12730128]
 23. Nagase H. Substrate specificity of MMPs. *Matrix Met Inhib Cancer Ther.* 2001; :39–66. DOI: 10.1007/978-1-59259-011-7_2
 24. Kim YS, Joh TH. Matrix metalloproteinases, new insights into the understanding of neurodegenerative disorders. *Biomol Ther.* 2012; 20:133–143. DOI: 10.4062/biomolther.2012.20.2.133
 25. Van Wart HE, Birkedal-Hansen H. The cysteine switch: a principle of regulation of metalloproteinase activity with potential applicability to the entire matrix metalloproteinase gene family. *Proc Natl Acad Sci U S A.* 1990; 87:5578–82. DOI: 10.1073/pnas.87.14.5578 [PubMed: 2164689]
 26. Grant GA, Eisen AZ, Marmer BL, Roswit WT, Goldberg GI. The activation of human skin fibroblast procollagenase. Sequence identification of the major conversion products. *J Biol Chem.* 1987; 262:5886–5889. [PubMed: 3032947]
 27. Springman EB, Angleton EL, Birkedal-Hansen H, Van Wart HE. Multiple modes of activation of latent human fibroblast collagenase: evidence for the role of a Cys73 active-site zinc complex in latency and a “cysteine switch” mechanism for activation. *Proc Natl Acad Sci U S A.* 1990; 87:364–368. DOI: 10.1073/pnas.87.1.364 [PubMed: 2153297]
 28. Mazzone M, Baldassarre M, Bezoussenko G, Giacchetti G, Cao J, Zucker S, Luini A, Buccione R. Intracellular processing and activation of membrane type 1 matrix metalloprotease depends on its partitioning into lipid domains. *J Cell Sci.* 2004; 117:6275–87. DOI: 10.1242/jcs.01563 [PubMed: 15561768]
 29. Sato H, Takino T, Kinoshita T, Imai K, Okada Y, Stevenson WG, Seiki M. Cell-Surface Binding and Activation of Gelatinase-A Induced by Expression of Membrane-Type-1-Matrix Metalloproteinase (Mt1-MMP). *FEBS Lett.* 1996; 385:238–240. [PubMed: 8647259]
 30. Murphy G, Stanton H, Cowell S, Butler G, Knäuper V, Atkinson S, Gavrilovic J. Mechanisms for pro matrix metalloproteinase activation. *APMIS.* 1999; 107:38–44. DOI: 10.1111/j.1699-0463.1999.tb01524.x [PubMed: 10190278]
 31. Sato H, Kinoshita T, Takino T, Nakayama K, Seiki M. Activation of a recombinant membrane type 1-matrix metalloproteinase (MT1-MMP) by furin and its interaction with tissue inhibitor of metalloproteinases (TIMP)-2. *FEBS Lett.* 1996; 393:101–104. DOI: 10.1016/0014-5793(96)00861-7 [PubMed: 8804434]
 32. Fanjul-Fernandez M, Folgueras AR, Cabrera S, Lopez-Otin C. Matrix metalloproteinases: evolution, gene regulation and functional analysis in mouse models. *Biochim Biophys Acta.* 2010; 1803:3–19. [pii]. DOI: 10.1016/j.bbamcr.2009.07.004 [PubMed: 19631700]
 33. Pei D, Weiss SJ. Furin-dependent intracellular activation of the human stromelysin-3 zymogen. *Nature.* 1995; 375:244–247. DOI: 10.1038/375244a0 [PubMed: 7746327]
 34. Ahokas K, Lohi J, Lohi H, Elomaa O, Karjalainen-Lindsberg ML, Kere J, Saarialho-Kere U. Matrix metalloproteinase-21, the human orthologue for XMMP, is expressed during fetal development and in cancer. *Gene.* 2002; 301:31–41. DOI: 10.1016/S0378-1119(02)01088-0 [PubMed: 12490321]
 35. Nagase H, Enghild JJ, Suzuki K, Salvesen G. Stepwise activation mechanisms of the precursor of matrix metalloproteinase 3 (stromelysin) by proteinases and (4-aminophenyl)mercuric acetate. *Biochemistry.* 1990; 29:5783–9. DOI: 10.1021/bi00476a020 [PubMed: 2383557]
 36. Ramos-Desimone N, Hahn-Dantona E, Siple J, Nagase H, French DL, Quigley JP. Activation of Matrix Metalloproteinase-9 (MMP-9) via a Converging Plasmin/Stromelysin-1 Cascade

- Enhances Tumor Cell Invasion. *Biochemistry*. 1999; 274:13066–13076. DOI: 10.1074/jbc.274.19.13066
37. Sims JD, McCready J, Jay DG. Extracellular heat shock protein (Hsp)70 and Hsp90a assist in matrix metalloproteinase-2 activation and breast cancer cell migration and invasion. *PLoS One*. 2011; 6doi: 10.1371/journal.pone.0018848
 38. Kinoh H, Sato H, Tsunozuka Y, Takino T, Kawashima A, Okada Y, Seiki M. MT-MMP, the cell surface activator of proMMP-2 (pro-gelatinase A), is expressed with its substrate in mouse tissue during embryogenesis. *J Cell Sci*. 1996; 109:953–959. [PubMed: 8743942]
 39. Jacob-Ferreira ALB, Passos CJS, Jordão AA, Fillion M, Mergler D, Lemire M, Gerlach RF, Barbosa F, Tanus-Santos JE. Mercury exposure increases circulating net matrix metalloproteinase (MMP)-2 and MMP-9 activities. *Basic Clin Pharmacol Toxicol*. 2009; 105:281–288. DOI: 10.1111/j.1742-7843.2009.00443.x [PubMed: 19594729]
 40. Lu P, Takai K, Weaver VM, Werb Z. Extracellular matrix degradation and remodeling in development and disease. *Cold Spring Harb Perspect Biol*. 2011; 3:1–24. DOI: 10.1101/cshperspect.a005058
 41. Morgunova E, Tuuttila A, Bergmann U, Tryggvason K, Huber R. Structural insight into the complex formation of latent matrix metalloproteinase 2 with tissue inhibitor of metalloproteinase 2. *Proc Natl Acad Sci U S A*. 2002; 99:7414–9. DOI: 10.1073/pnas.102185399 [PubMed: 12032297]
 42. Thorsen SB, Christensen SL, Würtz SO, Lundberg M, Nielsen BS, Vinther L, Knowles M, Gee N, Fredriksson S, Møller S, Brünner N, Schrohl AS, Stenvang J. Plasma levels of the MMP-9:TIMP-1 complex as prognostic biomarker in breast cancer: a retrospective study. *BMC Cancer*. 2013; 13:598.doi: 10.1186/1471-2407-13-598 [PubMed: 24330623]
 43. Koyama S. Intracellular localization of matrix metalloproteinases and their inhibitors in cultured tumor cell lines: Flow cytometric analysis. *Oncol Rep*. 2006; 15:735–738. [PubMed: 16465438]
 44. Soslau G, Mason C, Lynch S, Benjamin J, Ashak D, Prakash JM, Moore A, Bagsiyao P, Albert T, Mathew LM, Jost M. Intracellular matrix metalloproteinase-2 (MMP-2) regulates human platelet activation via hydrolysis of talin. *Thromb Haemost*. 2013; 111:140–153. DOI: 10.1160/TH13-03-0248 [PubMed: 24136115]
 45. Lovett DH, Mahimkar R, Raffai RL, Cape L, Maklashina E, Cecchini G, Karliner JS. A novel intracellular isoform of matrix metalloproteinase-2 induced by oxidative stress activates innate immunity. *PLoS One*. 2012; 7doi: 10.1371/journal.pone.0034177
 46. Pereda MP, Ledda MF, Goldberg V, Chervin A, Carrizo G, Molina H, Müller A, Renner U, Podhajcer O, Arzt E, Stalla GK. High levels of matrix metalloproteinases regulate proliferation and hormone secretion in pituitary cells. *J Clin Endocrinol Metab*. 2000; 85:263–269. DOI: 10.1210/jc.85.1.263 [PubMed: 10634397]
 47. Fernandez-Patron C, Zouki C, Whittall R. Matrix metalloproteinases regulate neutrophil-endothelial cell adhesion through generation of. *FASEB J*. 2001; 15:2230–2240. [PubMed: 11641250]
 48. Giannelli G, Falk-Marzillier J, Schiraldi O, Stetler-Stevenson WG, Quaranta V. Induction of cell migration by matrix metalloproteinase-2 cleavage of laminin-5. *Science (80-)*. 1997; 277:225–228. DOI: 10.1126/science.277.5323.225
 49. Kim JH, Kim JH, Cho CS, Jun HO, Kim DH, Yu YS, Kim KW. Differential roles of matrix metalloproteinase-9 and -2, depending on proliferation or differentiation of retinoblastoma cells. *Investig Ophthalmol Vis Sci*. 2010; 51:1783–1788. DOI: 10.1167/iovs.09-3990 [PubMed: 19933182]
 50. Augustin S, Berard M, Kellaf S, Peyri N, Fauvel-LAFÈVE F, Legrand C, He L, Crépin M. Matrix metalloproteinases are involved in both type I (Apoptosis) and type II (Autophagy) cell death induced by sodium phenylacetate in MDA-MB-231 breast tumour cells. *Anticancer Res*. 2009; 29:1335–1344. 29/4/1335 [pii]. [PubMed: 19414384]
 51. Manka SW, Carafoli F, Visse R, Bihan D, Raynal N, Farndale RW, Murphy G, Enghild JJ, Hohenester E, Nagase H. Structural insights into triple-helical collagen cleavage by matrix metalloproteinase 1. *Proc Natl Acad Sci U S A*. 2012; 109:12461–6. DOI: 10.1073/pnas.1204991109 [PubMed: 22761315]

52. Morrison CJ, Butler GS, Rodríguez D, Overall CM. Matrix metalloproteinase proteomics: substrates, targets, and therapy. *Curr Opin Cell Biol.* 2009; 21:645–653. DOI: 10.1016/j.ceb.2009.06.006 [PubMed: 19616423]
53. Greenlee KJ, Corry DB, Engler Da, Matsunami RK, Tessier P, Cook RG, Werb Z, Kheradmand F. Proteomic identification of in vivo substrates for matrix metalloproteinases 2 and 9 reveals a mechanism for resolution of inflammation. *J Immunol.* 2006; 177:7312–7321. 177/10/7312 [pii]. [PubMed: 17082650]
54. Fowlkes JL, Enghild JJ, Suzuki K, Nagase H. Matrix metalloproteinases degrade insulin-like growth factor-binding protein-3 in dermal fibroblast cultures. *J Biol Chem.* 1994; 269:25742–25746. [PubMed: 7523391]
55. Ito A, Mukaiyama A, Nagase H, Thøgersen IB, Jan J, Sasaguri Y, Mori Y, Itoh Y, Nagase H, Thøgersen IB, Enghild JJ, Sasaguri Y, Mori Y. Degradation of Interleukin 1 β by Matrix Metalloproteinases. *Journal.* 1996; 25:14657–14661. DOI: 10.1074/jbc.271.25.14657
56. Mucha A, Cuniasse P, Kannan R, Beau F, Yiotakis A, Basset P, Dive V. Membrane type-1 matrix metalloprotease and stromelysin-3 cleave more efficiently synthetic substrates containing unusual amino acids in their P1' positions. *J Biol Chem.* 1998; 273:2763–2768. DOI: 10.1074/jbc.273.5.2763 [PubMed: 9446583]
57. Pan W, Arnone M, Kendall M, Grafstrom RH, Seitz SP, Wasserman ZR, Albright CF. Identification of peptide substrates for human MMP-11 (stromelysin-3) using phage display. *J Biol Chem.* 2003; 278:27820–27827. DOI: 10.1074/jbc.M304436200 [PubMed: 12738779]
58. Kayano K, Shimada T, Shinomiya T, Nakai S, Hisa Y, Aoki T, Seiki M, Okada Y. Activation of pro-MMP-2 mediated by MT1-MMP in human salivary gland carcinomas: Possible regulation of pro-MMP-2 activation by TIMP-2. *J Pathol.* 2004; 202:403–411. DOI: 10.1002/path.1541 [PubMed: 15095267]
59. Mantuano E, Inoue G, Li X, Takahashi K, Gaultier A, Gonias SL, Campana WM. The Hemopexin Domain of Matrix Metalloproteinase-9 Activates Cell Signaling and Promotes Migration of Schwann Cells by Binding to Low-Density Lipoprotein Receptor- Related Protein. *Neuroscience.* 2008; 28:11571–11582. DOI: 10.1523/JNEUROSCI.3053-08.2008 [PubMed: 18987193]
60. Cox JH, Dean RA, Roberts CR, Overall CM. Matrix metalloproteinase processing of CXCL11/I-TAC results in loss of chemoattractant activity and altered glycosaminoglycan binding. *J Biol Chem.* 2008; 283:19389–19399. DOI: 10.1074/jbc.M800266200 [PubMed: 18411283]
61. Wong KK, Zhu F, Khatri I, Huo Q, Spaner DE, Gorczynski RM. Characterization of CD200 Ectodomain Shedding. *PLoS One.* 2016; 11:e0152073.doi: 10.1371/journal.pone.0152073 [PubMed: 27111430]
62. Tomlinson ML, Garcia-Morales C, Abu-Elmagd M, Wheeler GN. Three matrix metalloproteinases are required in vivo for macrophage migration during embryonic development. *Mech Dev.* 2008; 125:1059–1070. DOI: 10.1016/j.mod.2008.07.005 [PubMed: 18684398]
63. Swope VB, Boyce ST. Differential expression of matrix metalloproteinase-1 in vitro corresponds to tissue morphogenesis and quality assurance of cultured skin substitutes. *J Surg Res.* 2005; 128:79–86. DOI: 10.1016/j.jss.2005.03.018 [PubMed: 15936034]
64. Gaffney J, Solomonov I, Zehorai E, Sagi I. Multilevel regulation of matrix metalloproteinases in tissue homeostasis indicates their molecular specificity in vivo. *Matrix Biol.* 2014; 44–46:191–199. DOI: 10.1016/j.matbio.2015.01.012
65. Stevens LJ, Page-McCaw A. A secreted MMP is required for reepithelialization during wound healing. *Mol Biol Cell.* 2012; 23:1068–79. DOI: 10.1091/mbc.E11-09-0745 [PubMed: 22262460]
66. Burrage S, Peter. Matrix Metalloproteinases: Role in Arthritis. *Front Biosci.* 2006; 11:529.doi: 10.2741/1817 [PubMed: 16146751]
67. Agewall S. Matrix metalloproteinases and cardiovascular disease. *Eur Heart J.* 2006; 27:121–122. DOI: 10.1093/eurheartj/ehi639 [PubMed: 16272213]
68. McGarry Houghton A. Matrix metalloproteinases in destructive lung disease. *Matrix Biol.* 2015; 44–46:167–174. DOI: 10.1016/j.matbio.2015.02.002
69. Gialeli C, Theocharis AD, Karamanos NK. Roles of matrix metalloproteinases in cancer progression and their pharmacological targeting. *FEBS J.* 2011; 278:16–27. DOI: 10.1111/j.1742-4658.2010.07919.x [PubMed: 21087457]

70. Vu TH, Werb Z. Matrix metalloproteinases: Effectors of development and normal physiology. *Genes Dev.* 2000; 14:2123–2133. DOI: 10.1101/gad.815400 [PubMed: 10970876]
71. Löffek S, Schilling O, Franzke CW. Biological role of matrix metalloproteinases: A critical balance. *Eur Respir J.* 2011; 38:191–208. DOI: 10.1183/09031936.00146510 [PubMed: 21177845]
72. Rodríguez D, Morrison CJ, Overall CM. Matrix metalloproteinases: What do they not do? New substrates and biological roles identified by murine models and proteomics. *Biochim Biophys Acta - Mol Cell Res.* 2010; 1803:39–54. DOI: 10.1016/j.bbamcr.2009.09.015
73. Vandenbroucke RE, Libert C. Is there new hope for therapeutic matrix metalloproteinase inhibition? *Nat Rev Drug Discov.* 2014; 13:904–927. DOI: 10.1038/nrd4390 [PubMed: 25376097]
74. Dransfield DT, Devy L. New strategies for the next generation of matrix-metalloproteinase inhibitors: Selectively targeting membrane-anchored MMPs with therapeutic antibodies. *Biochem Res Int.* 2011; doi: 10.1155/2011/191670
75. Folgueras AR, Pendás AM, Sánchez LM, López-Otín C. Matrix metalloproteinases in cancer: From new functions to improved inhibition. *Int J Dev Biol.* 2004; 48:411–424. DOI: 10.1387/ijdb.041811af [PubMed: 15349816]
76. Page-Mccaw A, Ewald AJ, Werb Z. Matrix metalloproteinases and the regulation of tissue remodelling. *Nat Rev Mol Cell Biol.* 2007; 8:221–233. DOI: 10.1038/nrm2125.Matrix [PubMed: 17318226]
77. Annabi B, Lachambre M, Bousquet-Gagnon N, Pagé M, Gingras D, Béliveau R. Localization of membrane-type 1 matrix metalloproteinase in caveolae membrane domains. *Biochem J.* 2001; 353:547–53. DOI: 10.1042/0264-6021:3530547 [PubMed: 11171051]
78. Poola I, Dewitty RL, Marshallck JJ, Bhatnagar R, Abraham J, Leffall LD. Identification of MMP-1 as a putative breast cancer predictive marker by global gene expression analysis. *Nat Med.* 2005; 11:481–483. DOI: 10.1038/nm1243 [PubMed: 15864312]
79. Menshikov M, Elizarova E, Plakida K, Timofeeva A, Khaspekoy G, Beabealashvili R, Bobik A, Tkachuk V. Urokinase upregulates matrix metalloproteinase-9 expression in THP-1 monocytes via gene transcription and protein synthesis. *Biochem J.* 2002; 367:833–9. DOI: 10.1042/BJ20020663 [PubMed: 12117412]
80. Bachmeier B, Nerlich A, Lichtinghagen R, Sommerhoff C. Matrix metalloproteinases (MMPs) in breast cancer cell lines of different tumorigenicity. *Anticancer Res.* 2001; 21:3821–3828. [PubMed: 11911253]
81. Shah F. Clinical significance of matrix metalloproteinase 2 and 9 in breast cancer. *Indian J Cancer.* 2009; 46:194–202. DOI: 10.4103/0019-509X.52953 [PubMed: 19574670]
82. Jinga DC, Blidaru A, Condrea I, Ardeleanu C, Dragomir C, Szegli G, Stefanescu M, Matache C. MMP-9 and MMP-2 gelatinases and TIMP-1 and TIMP-2 inhibitors in breast cancer: Correlations with prognostic factors. *J Cell Mol Med.* 2006; 10:499–510. DOI: 10.1111/j.1582-4934.2006.tb00415.x [PubMed: 16796815]
83. Kubben FJ, Sier CF, Hawinkels LJ, Tschesche H, van Duijn W, Zuidwijk K, van der Reijden JJ, Hanemaaijer R, Griffioen G, Lamers CB, Verspaget HW. Clinical evidence for a protective role of lipocalin-2 against MMP-9 autodegradation and the impact for gastric cancer. *Eur J Cancer.* 2007; 43:1869–1876. DOI: 10.1016/j.ejca.2007.05.013 [PubMed: 17604154]
84. Park KJ, Hwang SC, Sheen SS, Oh YJ, Han JH, Lee KB. Expression of matrix metalloproteinase-9 in pleural effusions of tuberculosis and lung cancer. *Respiration.* 2005; 72:166–175. DOI: 10.1159/000084048 [PubMed: 15824527]
85. Jumper C, Cobos E, Lox C. Determination of the serum matrix metalloproteinase-9 (MMP-9) and tissue inhibitor of matrix metalloproteinase-1 (TIMP-1) in patients with either advanced small-cell lung cancer or non-small-cell lung cancer prior to treatment. *Respir Med.* 2004; 98:173–177. DOI: 10.1016/j.rmed.2003.08.014 [PubMed: 14971882]
86. Vasaturo F, Solai F, Malacrino C, Nardo T, Vincenzi B, Modesti M, Scarpa S. Plasma levels of matrix metalloproteinases 2 and 9 correlate with histological grade in breast cancer patients. *Oncol Lett.* 2012; 5:316–320. DOI: 10.3892/ol.2012.977 [PubMed: 23255941]
87. Yabushita H, Shimazu M, Noguchi M, Kishida T, Narumiya H, Sawagauchi K, Noguchi M. Vascular endothelial growth factor activating matrix metalloproteinase in ascitic fluid during

- peritoneal dissemination of ovarian cancer. *Oncol Rep.* 2003; 10:89–95. DOI: 10.3892/or.10.1.89 [PubMed: 12469150]
88. Ali-Labib R, Louka ML, Galal IH, Tarek M. Evaluation of matrix metalloproteinase-2 in lung cancer. *Proteomics - Clin Appl.* 2014; 8:251–257. DOI: 10.1002/prca.201300086 [PubMed: 24415566]
 89. Kuhlmann KFD, Van Till JWO, Boermeester MA, De Reuver PR, Tzvetanova ID, Offerhaus GJA, Ten Kate FJW, Busch ORC, Van Gulik TM, Gouma DJ, Crawford HC. Evaluation of matrix metalloproteinase 7 in plasma and pancreatic juice as a biomarker for pancreatic cancer. *Cancer Epidemiol Biomarkers Prev.* 2007; 16:886–891. DOI: 10.1158/1055-9965.EPI-06-0779 [PubMed: 17507610]
 90. Mohammed MA, Seleim MF, Abdalla MS, Sharada HM, Abdel Wahab AHA. Urinary high molecular weight matrix metalloproteinases as non-invasive biomarker for detection of bladder cancer. *BMC Urol.* 2013; 13:25.doi: 10.1186/1471-2490-13-25 [PubMed: 23672427]
 91. Wang HP, Wang YY, Pan J, Cen R, Cai YK. Evaluation of specific fecal protein biochips for the diagnosis of colorectal cancer. *World J Gastroenterol.* 2014; 20:1332–1339. DOI: 10.3748/wjg.v20.i5.1332 [PubMed: 24574808]
 92. Samara K, Giannarakis I, Papanikoalou I, Lambiri I, Siafakas N, Antoniou K. Overexpression of matrix metalloproteinase-7 (MMP-7) in bronchoalveolar lavage fluid (BALF) of IPF and lung cancer patients. *Eur Respir J.* 2011; 38:4761.
 93. Mannello F, Sebastiani M. Zymographic analyses and measurement of matrix metalloproteinase-2 and -9 in nipple aspirate fluids. *Clin Chem.* 2003; 49:1546–1550. DOI: 10.1373/49.9.1546 [PubMed: 12928245]
 94. Friedberg M, Glantz M, Klempner M, Cole B, Perides G. Specific matrix metalloproteinase profiles in the cerebrospinal fluid correlated with the presence of malignant astrocytomas, brain metastases, and carcinomatous meningitis. *Cancer.* 1998; 82:923–930. [PubMed: 9486583]
 95. Tutton MG, George ML, Eccles SA, Burton S, Swift RI, Abulafi AM. Use of plasma MMP-2 and MMP-9 levels as a surrogate for tumour expression in colorectal cancer patients. *Int J Cancer.* 2003; 107:541–550. DOI: 10.1002/ijc.11436 [PubMed: 14520690]
 96. Zhang G, Miyake M, Lawton A, Goodison S, Rosser CJ. Matrix metalloproteinase-10 promotes tumor progression through regulation of angiogenic and apoptotic pathways in cervical tumors. *BMC Cancer.* 2014; 14:310.doi: 10.1186/1471-2407-14-310 [PubMed: 24885595]
 97. Deryugina EI, Bourdon MA, Luo GX, Reisfeld RA, Strongin A. Matrix metalloproteinase-2 activation modulates glioma cell migration. *J Cell Sci.* 1997; 110:2473–2482. [PubMed: 9410885]
 98. Liu G, Atteridge CL, Wang X, Lundgren AD, Wu JD. The membrane type matrix metalloproteinase MMP14 mediates constitutive shedding of MHC class I chain-related molecule A independent of A disintegrin and metalloproteinases. *J Immunol.* 2010; 184:3346–3350. DOI: 10.4049/jimmunol.0903789 [PubMed: 20208009]
 99. Daniele A, Zito AF, Giannelli G, Divella R, Asselti M, Mazzocca A, Paradiso A, Quaranta M. Expression of metalloproteinases MMP-2 and MMP-9 in sentinel lymph node and serum of patients with metastatic and non-metastatic breast cancer. *Anticancer Res.* 2010; 30:3521–3527. [PubMed: 20944132]
 100. Wu K, Fukuda K, Xing F, Zhang Y, Sharma S, Liu Y, Chan MD, Zhou X, Qasem SA, Pochampally R, Mo YY, Watabe K. Roles of the cyclooxygenase 2 matrix metalloproteinase 1 pathway in brain metastasis of breast cancer. *J Biol Chem.* 2015; 290:9842–9854. DOI: 10.1074/jbc.M114.602185 [PubMed: 25691572]
 101. Zheng J, Chu D, Wang D, Zhu Y, Zhang X, Ji G, Zhao H, Wu G, Du J, Zhao Q. Matrix metalloproteinase-12 is associated with overall survival in Chinese patients with gastric cancer. *J Surg Oncol.* 2013; 107:746–751. DOI: 10.1002/jso.23302 [PubMed: 23280473]
 102. Wu T, Li Y, Lu J, Qiao Q, Bao G, Wang N, He X, Du X. Increased MMP-21 expression is associated with poor overall survival of patients with gastric cancer. *Med Oncol.* 2013; 30:323.doi: 10.1007/s12032-012-0323-8 [PubMed: 23275114]
 103. Hwang T-L, Lee L-Y, Wang C-C, Liang Y, Huang S-F, Wu C-M. Claudin-4 expression is associated with tumor invasion, MMP-2 and MMP-9 expression in gastric cancer. *Exp Ther Med.* 2010; 1:789–797. DOI: 10.3892/etm.2010.116 [PubMed: 22993603]

104. Yang B, Gao J, Rao Z, Shen Q. Clinicopathological significance and prognostic value of MMP-13 expression in colorectal cancer. *Scand J Clin Lab Invest.* 2012; 72:501–505. DOI: 10.3109/00365513.2012.699638 [PubMed: 22950625]
105. Leinonen T, Pirinen R, Böhm J, Johansson R, Kosma VM. Increased expression of matrix metalloproteinase-2 (MMP-2) predicts tumour recurrence and unfavourable outcome in non-small cell lung cancer. *Histol Histopathol.* 2008; 23:693–700. DOI: 10.14670/HH-23.693 [PubMed: 18366007]
106. Wang YZ, Wu KP, Wu AB, Yang ZC, Li JM, Mo YL, Xu M, Wu B, Yang ZX. MMP-14 overexpression correlates with poor prognosis in non-small cell lung cancer. *Tumor Biol.* 2014; 35:9815–9821. DOI: 10.1007/s13277-014-2237-x
107. Schleifman EB, Desai R, Spoerke JM, Xiao Y, Wong C, Abbas I, O'Brien C, Patel R, Sumiyoshi T, Fu L, Tam RN, Koeppen H, Wilson TR, Raja R, Hampton GM, Lackner MR. Targeted biomarker profiling of matched primary and metastatic estrogen receptor positive breast cancers. *PLoS One.* 2014; 9:1–12. DOI: 10.1371/journal.pone.0088401
108. Vecchi M, Confalonieri S, Nuciforo P, Viganò Ma, Capra M, Bianchi M, Nicosia D, Bianchi F, Galimberti V, Viale G, Palermo G, Riccardi a, Campanini R, Daidone MG, Pierotti Ma, Pece S, Di Fiore PP. Breast cancer metastases are molecularly distinct from their primary tumors. *Oncogene.* 2008; 27:2148–2158. DOI: 10.1038/sj.onc.1210858 [PubMed: 17952122]
109. Torres L, Ribeiro FR, Pandis N, Andersen JA, Heim S, Teixeira MR. Intratumor genomic heterogeneity in breast cancer with clonal divergence between primary carcinomas and lymph node metastases. *Breast Cancer Res Treat.* 2007; 102:143–155. DOI: 10.1007/s10549-006-9317-6 [PubMed: 16906480]
110. Schmidt-Kittler O, Ragg T, Daskalakis A, Granzow M, Ahr A, Blankenstein TJF, Kaufmann M, Diebold J, Arnholdt H, Muller P, Bischoff J, Harich D, Schlimok G, Riethmuller G, Eils R, Klein CA. From latent disseminated cells to overt metastasis: genetic analysis of systemic breast cancer progression. *Proc Natl Acad Sci U S A.* 2003; 100:7737–42. DOI: 10.1073/pnas.1331931100 [PubMed: 12808139]
111. Figueira RCS, Gomes LR, Neto JS, Silva FC, Silva IDCG, Sogayar MC. Correlation between MMPs and their inhibitors in breast cancer tumor tissue specimens and in cell lines with different metastatic potential. *BMC Cancer.* 2009; 9:20.doi: 10.1186/1471-2407-9-20 [PubMed: 19144199]
112. Cheng H, Wang L, Mollica M, Re AT, Wu S, Zuo L. Nitric oxide in cancer metastasis. *Cancer Lett.* 2014; 353:1–7. DOI: 10.1016/j.canlet.2014.07.014 [PubMed: 25079686]
113. Deryugina EI, Quigley JP. Matrix metalloproteinases and tumor metastasis. *Cancer Metastasis Rev.* 2006; 25:9–34. DOI: 10.1007/s10555-006-7886-9 [PubMed: 16680569]
114. Rempe RG, Hartz AM, Bauer B. Matrix metalloproteinases in the brain and blood–brain barrier: Versatile breakers and makers. *J Cereb Blood Flow Metab.* 2016; 36:1481–1507. DOI: 10.1177/0271678X16655551 [PubMed: 27323783]
115. Egeblad M, Werb Z. New functions for the matrix metalloproteinases in cancer progression. *Nat Rev Cancer.* 2002; 2:161–174. DOI: 10.1038/nrc745 [PubMed: 11990853]
116. Fingleton B, Lynch CC, Vargo-Gogola T, Matrisian LM. Cleavage of E-cadherin by matrix metalloproteinase-7 promotes cellular proliferation in nontransformed cell lines via activation of RhoA. *J Oncol.* 2010; 2010:530745.doi: 10.1155/2010/530745 [PubMed: 20628524]
117. Chen PS, Shih YW, Huang HC, Cheng HW. Diosgenin, a steroidal saponin, inhibits migration and invasion of human prostate cancer pc-3 cells by reducing matrix metalloproteinases expression. *PLoS One.* 2011; 6:1–10. DOI: 10.1371/journal.pone.0020164
118. Chan KT, Cortesio CL, Huttenlocher A. Fak alters invadopodia and focal adhesion composition and dynamics to regulate breast cancer invasion. *J Cell Biol.* 2009; 185:357–370. DOI: 10.1083/jcb.200809110 [PubMed: 19364917]
119. Oskarsson T. Extracellular matrix components in breast cancer progression and metastasis. *Breast.* 2013; 22:S66–72. DOI: 10.1016/j.breast.2013.07.012 [PubMed: 24074795]
120. Ribeiro AS, Carvalho FA, Figueiredo J, Carvalho R, Mestre T, Monteiro J, Guedes AF, Fonseca M, Sanches J, Seruca R, Santos NC, Paredes J. Atomic force microscopy and graph analysis to

study the P-cadherin/SFK mechanotransduction signalling in breast cancer cells. *Nanoscale*. 2016; 8:19390–19401. DOI: 10.1039/C6NR04465D [PubMed: 27847941]

121. Kim SH, Turnbull J, Guimond S. Extracellular matrix and cell signalling: The dynamic cooperation of integrin, proteoglycan and growth factor receptor. *J Endocrinol*. 2011; 209:139–151. DOI: 10.1530/JOE-10-0377 [PubMed: 21307119]
122. Juncker-Jensen A, Deryugina EI, Rimann I, Zajac E, Kupriyanova TA, Engelholm LH, Quigley JP. Tumor MMP-1 activates endothelial PAR1 to facilitate vascular intravasation and metastatic dissemination. *Cancer Res*. 2013; 73:4196–4211. DOI: 10.1158/0008-5472.CAN-12-4495 [PubMed: 23687338]
123. Hummel V, Kallmann BA, Wagner S, Fuller T, Bayas A, Tonn JC, Benveniste EN, Toyka KV, Rieckmann P. Production of MMPs in human cerebral endothelial cells and their role in shedding adhesion molecules. *J Neuropathol Exp Neurol*. 2001; 60:320–327. [PubMed: 11305867]
124. Strell C, Entschladen F. Extravasation of leukocytes in comparison to tumor cells. *Cell Commun Signal*. 2008; 6:10. doi: 10.1186/1478-811X-6-10 [PubMed: 19055814]
125. Leong HS, Robertson AE, Stoletov K, Leith SJ, Chin CA, Chien AE, Hague MN, Ablack A, Carmine-Simmen K, McPherson VA, Postenka CO, Turley EA, Courtneidge SA, Chambers AF, Lewis JD. Invadopodia Are Required for Cancer Cell Extravasation and Are a Therapeutic Target for Metastasis. *Cell Rep*. 2014; 8:1558–1570. DOI: 10.1016/j.celrep.2014.07.050 [PubMed: 25176655]
126. Nakamura H, Suenaga N, Taniwaki K, Matsuki H, Yonezawa K, Fujii M, Okada Y, Seiki M. Constitutive and Induced CD44 Shedding by ADAM-Like Proteases and Membrane-Type 1 Matrix Metalloproteinase. *Cancer Res*. 2004; 64:876–882. DOI: 10.1158/0008-5472.CAN-03-3502 [PubMed: 14871815]
127. Wolf K, te Lindert M, Krause M, Alexander S, te Riet J, Willis AL, Hoffman RM, Figdor CG, Weiss SJ, Friedl P. Physical limits of cell migration: Control by ECM space and nuclear deformation and tuning by proteolysis and traction force. *J Cell Biol*. 2013; 201:1069–1084. DOI: 10.1083/jcb.201210152 [PubMed: 23798731]
128. Marchenko ND, Marchenko GN, Weinreb RN, Lindsey JD, Kyshtoobayeva A, Crawford HC, Strongin AY. B-Catenin regulates the gene of MMP-26, a novel matrix metalloproteinase expressed both in carcinomas and normal epithelial cells. *Int J Biochem Cell Biol*. 2004; 36:942–956. DOI: 10.1016/j.biocel.2003.12.007 [PubMed: 15006646]
129. Solli AI, Fadnes B, Winberg J-O, Uhlin-Hansen L, Hadler-Olsen E. Tissue- and Cell-Specific Co-localization of Intracellular Gelatinolytic Activity and Matrix Metalloproteinase 2. *J Histochem Cytochem*. 2013; 61:444–461. DOI: 10.1369/0022155413484765 [PubMed: 23482328]
130. Aldonyte R, Brantly M, Block E, Patel J, Zhang J. Nuclear localization of active matrix metalloproteinase-2 in cigarette smoke-exposed apoptotic endothelial cells. *Exp Lung Res*. 2009; 35:59–75. DOI: 10.1080/01902140802406059 [PubMed: 19191105]
131. Hadler-Olsen E, Ljones H, Ravuri C, Omair A. Organ specific regulation of tumour invasiveness and gelatinolytic activity at the invasive front. *Eur J Cancer*. 2011; 47:305–315. DOI: 10.1016/j.ejca.2010.09.006 [PubMed: 20932741]
132. Si-tayeb K, Monvoisin A, Decossas M, Robinson DR, Rosenbaum J. Matrix Metalloproteinase 3 is Present in the Cell Nucleus and is Involved in Apoptosis. *Tumorigenes Neoplast Progress*. 2006; 169:1390–1401. DOI: 10.2353/ajpath.2006.060005
133. Choi DH, Kim E-M, Son HJ, Joh TH, Kim YS, Kim D, Beal MF, Hwang O. A novel intracellular role of matrix metalloproteinase-3 during apoptosis of dopaminergic cells. *J Neurochem*. 2008; 106:405–415. DOI: 10.1111/j.1471-4159.2008.05399.x [PubMed: 18397366]
134. Mehner C, Miller E, Nassar A, Bamlet WR, Evette S, Radisky DC. Tumor cell expression of MMP3 as a prognostic factor for poor survival in pancreatic, pulmonary, and mammary carcinoma. *Genes Cancer*. 2015; 6:480–489. [PubMed: 26807201]
135. Cauwe B, Opdenakker G. Intracellular substrate cleavage : a novel dimension in the biochemistry, biology and pathology of matrix - metalloproteinases. *Crit Rev Biochem Mol Biol*. 2010; 45:351–423. DOI: 10.3109/10409238.2010.501783 [PubMed: 20812779]
136. Hockenbery DM. MMPs in Unusual Places. *Am J Pathol*. 2006; 169:1101–1103. DOI: 10.2353/ajpath.2006.060553 [PubMed: 17003469]

137. Fridman R, Toth M, Chvyrkova I, Meroueh SO, Mobashery S. Cell surface association of matrix metalloproteinase-9 (gelatinase B). *Cancer Metastasis Rev.* 2003; 22:153–166. [PubMed: 12784994]
138. Mira E, Lacalle RA, Buesa JM, De Buitrago GG, Jiménez-Baranda S, Gómez-Moutón C, Martínez-a C, Mañes S. Secreted MMP9 promotes angiogenesis more efficiently than constitutive active MMP9 bound to the tumor cell surface. *J Cell Sci.* 2004; 117:1847–1856. DOI: 10.1242/jcs.01035 [PubMed: 15075244]
139. Mannello F, Medda V. Nuclear localization of matrix metalloproteinases. *Prog Histochem Cytochem.* 2012; 47:27–58. DOI: 10.1016/j.proghi.2011.12.002 [PubMed: 22226510]
140. Roderfeld M, Graf J, Giese B, Salguero-Palacios R, Tschuschner A, Muller-Newen G, Roeb E. Latent MMP-9 is bound to TIMP-1 before secretion. *J Biol Chem.* 2007; 388:1227–1234. DOI: 10.1515/BC.2007.123
141. Bornschein J, Seidel T, Langner C, Link A, Wex T, Selgrad M, Jechorek D, Meyer F, Bird-lieberman E, Vieth M, Malfertheiner P. MMP2 and MMP7 at the invasive front of gastric cancer are not associated with mTOR expression. *Diagn Pathol.* 2015; 10:212.doi: 10.1186/s13000-015-0449-z [PubMed: 26652716]
142. Gonzalez LO, Gonzalez-Reyes S, Marin L, Gonzalez L, Gonzalez JM, Lamelas ML, Merino AM, Rodr E, Casar M, Andicoechea A, Vizoso F. Comparative analysis and clinical value of the expression of metalloproteases and their inhibitors by intratumour stromal mononuclear inflammatory cells and those at the invasive front of breast carcinomas. *Histopathology.* 2010; 57:862–876. DOI: 10.1111/j.1365-2559.2010.03723.x [PubMed: 21166700]
143. Fu XR, Zhang C, Chen CY, Zhang L, Wang LX, Wang BH, Liu XY, Zhang MZ. Expression and significance of matrix metalloproteinase and tissue inhibitor of matrix metalloproteinase in non-melanoma skin cancer. *Chinese J Oncol.* 2012; 34:369–373. DOI: 10.3760/cma.j.issn.0253-3766.2012.05.011
144. Illemann M, Bird N, Majeed A, Sehested M, Laerum OD, Lund LR, Danø K, Nielsen BS. MMP-9 Is Differentially Expressed in Primary Human Colorectal Adenocarcinomas and Their Metastases. *Mol Cancer Res.* 2006; 4:293–302. DOI: 10.1158/1541-7786.MCR-06-0003 [PubMed: 16687484]
145. Eiró N, Fernandez-García B, Vázquez J, Casar JM, Luis O, Vizoso FJ. A phenotype from tumor stroma based on the expression of metalloproteases and their inhibitors, associated with prognosis in breast cancer A phenotype from tumor stroma based on the expression of metalloproteases and their inhibitors, associated with pr. *Oncoimmunology.* 2015; 4:e992222.doi: 10.4161/2162402X.2014.992222 [PubMed: 26140253]
146. Kahlert C, Bandapalli OR, Schirmacher P, Weitz J, Brand K. Invasion Front-specific Overexpression of Tissue Inhibitor of Metalloproteinase-1 in Liver Metastases from Colorectal Cancer. *Anticancer Res.* 2008; 28:1459–1465. [PubMed: 18630499]
147. Calascibetta A, Gebbia V, Cabibi D, Martorana A, Aragona F, Rausa L, Sanguedolce R. Matrix metalloproteinase-1 is differentially expressed in signet ring cell, and intestinal colorectal carcinoma histotypes. *J Clin Oncol.* 2007; 25:14564.doi: 10.1200/jco.2007.25.18_suppl.14564
148. García MF, González-Reyes S, González LO, Junquera S, Berdize N, Del Casar JM, Medina M, Vizoso FJ. Comparative study of the expression of metalloproteases and their inhibitors in different localizations within primary tumours and in metastatic lymph nodes of breast cancer. *Int J Exp Pathol.* 2010; 91:324–334. DOI: 10.1111/j.1365-2613.2010.00709.x [PubMed: 20412339]
149. Suarez-Roa ML, Asbun-Bojalil J, Ruiz-Godoy LM, Meneses-García AA. Immunoexpression of matrix metalloproteinases and their inhibitors in different areas of oral squamous cell carcinoma. *Aust Dent J.* 2012; 57:300–307. DOI: 10.1111/j.1834-7819.2012.01705.x [PubMed: 22924352]
150. Kajiwara Y, Ueno H, Hashiguchi Y, Shinto E, Shimazaki H, Mochizuki H, Hase K. Heterogeneity of metalloproteinase expression in colorectal cancer - Relation of molecular findings to basic morphology. *Anticancer Res.* 2011; 31:1567–1575. [PubMed: 21617211]
151. Eiró N, Pidal I, Fernandez-García B, Junquera S, Lamelas ML, del Casar JM, González LO, López-Muñiz A, Vizoso FJ. Impact of CD68/(CD3+CD20) Ratio at the Invasive Front of Primary Tumors on Distant Metastasis Development in Breast Cancer. *PLoS One.* 2012; 7:e52796.doi: 10.1371/journal.pone.0052796 [PubMed: 23300781]

152. Barros SSLV, Henriques ÁCG, Pereira KMA, De Medeiros AMC, Galvão HC, Freitas RDA. Immunohistochemical expression of matrix metalloproteinases in squamous cell carcinoma of the tongue and lower lip. *Arch Oral Biol.* 2011; 56:752–760. DOI: 10.1016/j.archoralbio.2010.11.022 [PubMed: 21255765]
153. Johansson N, Vaalamo M, Grénman S, Hietanen S, Klemi P, Saarialho-Kere U, Kähäri VM. Collagenase-3 (MMP-13) is expressed by tumor cells in invasive vulvar squamous cell carcinomas. *Am J Pathol.* 1999; 154:469–480. DOI: 10.1016/S0002-9440(10)65293-5 [PubMed: 10027405]
154. Impola U, Uitto VJ, Hietanen J, Hakkinen L, Zhang L, Larjava H, Isaka K, Saarialho-Kere U. Differential expression of matrilysin-I (MMP-7), 92 kD gelatinase (MMP-9), and metalloelastase (MMP-12) in oral verrucous and squamous cell cancer. *J Pathol.* 2004; 202:14–22. DOI: 10.1002/path.1479 [PubMed: 14694517]
155. Barajas-Castañeda LM, Cortés-Gutiérrez E, García-Rodríguez FM, Campos-Rodríguez R, Lara-Padilla E, Enríquez-Rincón F, Castro-Mussot ME, Figueroa-Arredondo P. Overexpression of MMP-3 and uPA with Diminished PAI-1 Related to Metastasis in Ductal Breast Cancer Patients Attending a Public Hospital in Mexico City. *J Immunol Res.* 2016; 2016:8519648.doi: 10.1155/2016/8519648 [PubMed: 27975070]
156. Collier IE, Legant W, Marmer B, Lubman O, Saffarian S, Wakatsuki T, Elson E, Goldberg GI. Diffusion of MMPs on the surface of collagen fibrils: The mobile cell surface - collagen substratum interface. *PLoS One.* 2011; 6:e24029.doi: 10.1371/journal.pone.0024029 [PubMed: 21912660]
157. Weidle UH, Tiefenthaler G, Georges G. Proteases as activators for cytotoxic prodrugs in antitumor therapy. *Cancer Genomics and Proteomics.* 2014; 11:67–80. [PubMed: 24709544]
158. Yang Y, Aloysius H, Inoyama D, Chen Y, Hu L. Enzyme-mediated hydrolytic activation of prodrugs. *Acta Pharm Sin B.* 2011; 1:143–159. DOI: 10.1016/j.apsb.2011.08.001
159. Vartak DG, Gemeinhart RA. Matrix metalloproteases: Underutilized targets for drug delivery. *J Drug Target.* 2007; 15:1–20. DOI: 10.1080/10611860600968967 [PubMed: 17365270]
160. Gustafson JA, Price RA, Frandsen J, Henak CR, Cappello J, Ghandehari H. Synthesis and characterization of a matrix-metalloproteinase responsive silk-elastinlike protein polymer. *Biomacromolecules.* 2013; 14:618–625. DOI: 10.1021/bm3013692 [PubMed: 23369048]
161. Price R, Poursaid A, Ghandehari H. Controlled release from recombinant polymers. *J Control Release.* 2014; 190:304–313. DOI: 10.1016/j.jconrel.2014.06.016 [PubMed: 24956486]
162. Gustafson J, Greish K, Frandsen J, Cappello J, Ghandehari H. Silk-elastinlike recombinant polymers for gene therapy of head and neck cancer: From molecular definition to controlled gene expression. *J Control Release.* 2009; 140:256–261. DOI: 10.1016/j.jconrel.2009.05.022 [PubMed: 19470397]
163. Huang W, Rollett A, Kaplan DL. Silk-elastin-like protein biomaterials for the controlled delivery of therapeutics. *Expert Opin Drug Deliv.* 2015; 12:779–791. DOI: 10.1517/17425247.2015.989830 [PubMed: 25476201]
164. Megeed Z, Haider M, Li D, O'Malley BW, Cappello J, Ghandehari H. In vitro and in vivo evaluation of recombinant silk-elastinlike hydrogels for cancer gene therapy. *J Control Release.* 2004; 94:433–445. DOI: 10.1016/j.jconrel.2003.10.027 [PubMed: 14744493]
165. Poursaid A, Price R, Tiede A, Olson E, Huo E, McGill L, Ghandehari H, Cappello J. In situ gelling silk-elastinlike protein polymer for transarterial chemoembolization. *Biomaterials.* 2015; 57:142–152. DOI: 10.1016/j.biomaterials.2015.04.015 [PubMed: 25916502]
166. Poursaid A, Jensen MM, Nourbakhsh I, Weisenberger M, Hellgeth JW, Sampath S, Cappello J, Ghandehari H. Silk-Elastinlike Protein Polymer Liquid Chemoembolic for Localized Release of Doxorubicin and Sorafenib. *Mol Pharm.* 2016; 13:2736–2748. DOI: 10.1021/acs.molpharmaceut.6b00325 [PubMed: 27295352]
167. Frandsen JL, Ghandehari H. Recombinant protein-based polymers for advanced drug delivery. *Chem Soc Rev.* 2012; 41:2696–2706. DOI: 10.1039/c2cs15303c [PubMed: 22344293]
168. Price R, Poursaid A, Cappello J, Ghandehari H. Effect of shear on physicochemical properties of matrix metalloproteinase responsive silk-elastinlike hydrogels. *J Control Release.* 2014; 195:92–98. DOI: 10.1016/j.jconrel.2014.07.044 [PubMed: 25094031]

169. Price R, Gustafson J, Greish K, Cappello J, McGill L, Ghandehari H. Comparison of silk-elastinlike protein polymer hydrogel and poloxamer in matrix-mediated gene delivery. *Int J Pharm.* 2012; 427:97–104. DOI: 10.1016/j.ijpharm.2011.09.037 [PubMed: 21982738]
170. Price R, Poursaid A, Cappello J, Ghandehari H. In vivo evaluation of matrix metalloproteinase responsive silk-elastinlike protein polymers for cancer gene therapy. *J Control Release.* 2015; 213:96–102. DOI: 10.1016/j.jconrel.2015.06.022 [PubMed: 26095079]
171. Tauro JR, Gemeinhart RA. Matrix Metalloproteinase Triggered Delivery of Cancer Chemotherapy from Hydrogel Matrixes. *Bioconjug Chem.* 2005; 16:1133–1139. [PubMed: 16173790]
172. Tauro JR, Lee BS, Lateef SS, Gemeinhart RA. Matrix metalloprotease selective peptide substrates cleavage within hydrogel matrices for cancer chemotherapy activation. *Peptides.* 2008; 29:1965–1973. DOI: 10.1016/j.peptides.2008.06.021 [PubMed: 18652863]
173. Zhang Y, Gemeinhart RA. Improving matrix metalloproteinase-2 specific response of a hydrogel system using electrophoresis. *Int J Pharm.* 2012; 429:31–37. DOI: 10.1016/j.ijpharm.2012.03.012 [PubMed: 22440150]
174. Ross AE, Tang MY, Gemeinhart Ra. Effects of Molecular Weight and Loading on Matrix Metalloproteinase-2 Mediated Release from Poly(Ethylene Glycol) Diacrylate Hydrogels. *AAPS J.* 2012; 14:482–490. DOI: 10.1208/s12248-012-9356-3 [PubMed: 22535508]
175. Chau Y, Tan FE, Langer R. Synthesis and characterization of dextran-peptide-methotrexate conjugates for tumor targeting via mediation by matrix metalloproteinase II and matrix metalloproteinase IX. *Bioconjug Chem.* 2004; 15:931–941. DOI: 10.1021/bc0499174 [PubMed: 15264885]
176. Kratz F, Dreves J, Bing G, Stockmar C, Scheuermann K, Lazar P, Unger C. Development and In Vitro Efficacy of Novel MMP2 and MMP9 Specific Doxorubicin Albumin Conjugates. *Bioorg Med Chem Lett.* 2001; 11:2001–2006. DOI: 10.1016/S0960-894X(01)00354-7 [PubMed: 11454467]
177. Mansour AM, Dreves J, Esser N, Hamada FM, Badary OA, Unger C, Fichtner I, Kratz F. A New Approach for the Treatment of Malignant Melanoma: Enhanced Antitumor Efficacy of an Albumin-binding Doxorubicin Prodrug That Is Cleaved by Matrix Metalloproteinase 2. *Cancer Res.* 2003; 63:4062–4066. <http://cancerres.aacrjournals.org/content/63/14/4062.full>. [PubMed: 12874007]
178. Chau Y, Padera RF, Dang NM, Langer R. Antitumor efficacy of a novel polymer-peptide-drug conjugate in human tumor xenograft models. *Int J Cancer.* 2006; 118:1519–1526. DOI: 10.1002/ijc.21495 [PubMed: 16187287]
179. Bae M, Cho S, Song J, Lee GY, Kim K, Yang J, Cho K, Kim SY, Byun Y. Metalloprotease-specific poly(ethylene glycol) methyl ether-peptide-doxorubicin conjugate for targeting anticancer drug delivery based on angiogenesis. *Drugs Exp Clin Res.* 2003; 29:15–23. [PubMed: 12866360]
180. Banerjee J, Hanson AJ, Gadani B, Elegbede AI, Tobwala S, Ganguly B, Wagh AV, Muhonen WW, Law B, Shabb JB, Srivastava DK, Mallik S. Release of liposomal contents by cell-secreted matrix metalloproteinase-9. *Bioconjug Chem.* 2009; 20:1332–1339. DOI: 10.1021/bc9000646 [PubMed: 19601658]
181. Kulkarni PS, Haldar MK, Nahire RR, Katti P, Ambre AH, Muhonen WW, Shabb JB, Padi SKR, Singh RK, Borowicz PP, Shrivastava DK, Katti KS, Reindl K, Guo B, Mallik S. MMP-9 responsive PEG cleavable nanovesicles for efficient delivery of chemotherapeutics to pancreatic cancer. *Mol Pharm.* 2014; 11:2390–2399. DOI: 10.1021/mp500108p [PubMed: 24827725]
182. Hua D, Kong W, Zheng X, Zhou Z, Yu B, Li Y, Wang Y, Yang X, Liu C, Tang L, Li Y, Gong M. Potent tumor targeting drug release system comprising MMP-2 specific peptide fragment with self-assembling characteristics. *Drug Des Devel Ther.* 2014; 8:1839–1849. DOI: 10.2147/DDDT.S67305
183. Gao W, Xiang B, Meng T, Liu F, Qi X. Chemotherapeutic drug delivery to cancer cells using a combination of folate targeting and tumor microenvironment-sensitive polypeptides. *Biomaterials.* 2013; 34:4137–49. DOI: 10.1016/j.biomaterials.2013.02.014 [PubMed: 23453200]
184. Zhu L, Wang T, Perche F, Taigind A, Torchilin VP. Enhanced anticancer activity of nanopreparation containing an MMP2-sensitive PEG-drug conjugate and cell-penetrating moiety.

Proc Natl Acad Sci U S A. 2013; 110:17047–52. DOI: 10.1073/pnas.1304987110 [PubMed: 24062440]

185. Li H, Yu SS, Miteva M, Nelson CE, Werfel T, Giorgio TD, Duvall CL. Matrix metalloproteinase responsive, proximity-activated polymeric nanoparticles for siRNA delivery. *Adv Funct Mater.* 2013; 23:3040–3052. DOI: 10.1002/adfm.201202215 [PubMed: 25214828]
186. Allen C, McDonald C, Giannini C, Peng K, Rosales G, Russell SJ, Galanis E. Adenoviral vectors expressing fusogenic membrane glycoproteins activated via matrix metalloproteinase cleavable linkers have significant antitumor potential in the gene therapy of gliomas. *J Gene Med.* 2004; 6:1216–1227. DOI: 10.1002/jgm.616 [PubMed: 15459967]
187. Holle L, Song W, Holle E, Wei Y, Wagner T, Yu X. A matrix metalloproteinase 2 cleavable melittin/avidin conjugate specifically targets tumor cells in vitro and in vivo. *Int J Oncol.* 2003; 22:93–98. [PubMed: 12469190]
188. Liu S, Wang H, Currie BM, Molinolo A, Leung HJ, Moayeri M, Basile JR, Alfano RW, Gutkind JS, Frankel AE, Bugge TH, Leppla SH. Matrix metalloproteinase-activated anthrax lethal toxin demonstrates high potency in targeting tumor vasculature. *J Biol Chem.* 2008; 283:529–540. DOI: 10.1074/jbc.M707419200 [PubMed: 17974567]
189. Ruan S, He Q, Gao H. Matrix metalloproteinase triggered size-shrinkable gelatin-gold fabricated nanoparticles for tumor microenvironment sensitive penetration and diagnosis of glioma. *Nanoscale.* 2015; 7:9487–9496. DOI: 10.1039/c5nr01408e [PubMed: 25909483]
190. Wong C, Stylianopoulos T, Cui J, Martin J, Chauhan VP, Jiang W, Popovic Z, Jain RK, Bawendi MG, Fukumura D. Multistage nanoparticle delivery system for deep penetration into tumor tissue. *Proc Natl Acad Sci.* 2011; 108:2426–2431. DOI: 10.1073/pnas.1018382108 [PubMed: 21245339]
191. Liu Y, Ding X, Li J, Luo Z, Hu Y, Liu J, Dai L, Zhou J, Hou C, Cai K. Enzyme responsive drug delivery system based on mesoporous silica nanoparticles for tumor therapy in vivo. *Nanotechnology.* 2015; 26:145102.doi: 10.1088/0957-4484/26/14/145102 [PubMed: 25789511]
192. Hu G, Wang Y, He Q, Gao H. Multistage drug delivery system based on microenvironment-responsive dendrimer–gelatin nanoparticles for deep tumor penetration. *RSC Adv.* 2015; 5:85933–85937. DOI: 10.1039/C5RA18833D
193. Ansari C, Tikhomirov GA, Hong SH, Falconer RA, Loadman PM, Gill JH, Castaneda R, Hazard FK, Tong L, Lenkov OD, Felsher DW, Rao J, Daldrop-Link HE. Development of novel tumor-targeted theranostic nanoparticles activated by membrane-type matrix metalloproteinases for combined cancer magnetic resonance imaging and therapy. *Small.* 2014; 10:566–575. DOI: 10.1002/sml.201301456 [PubMed: 24038954]
194. Liu TW, Akens MK, Chen J, Wilson BC, Zheng G. Matrix metalloproteinase-based photodynamic molecular beacons for targeted destruction of bone metastases in vivo. *Photochem Photobiol Sci.* 2016; 15:375–381. DOI: 10.1039/C5PP00414D [PubMed: 26880165]
195. Dragutinovi VV, Radovanovi NS, Izrael-Zivkovi LT, Vrvic MM. Detection of gelatinase B activity in serum of gastric cancer patients. *World J Gastroenterol.* 2006; 12:105–9. <http://www.ncbi.nlm.nih.gov/pubmed/16440426>. [PubMed: 16440426]
196. Koivunen E, Arap W, Valtanen H, Rainisalo a, Medina OP, Heikkilä P, Kantor C, Gahmberg CG, Salo T, Kontinen YT, Sorsa T, Ruoslahti E, Pasqualini R. Tumor targeting with a selective gelatinase inhibitor. *Nat Biotechnol.* 1999; 17:768–774. DOI: 10.1038/11703 [PubMed: 10429241]
197. Kawano T, Murata M, Piao JS, Narahara S, Hamano N, Kang JH, Hashizume M. Systemic delivery of protein nanocages bearing CTT peptides for enhanced imaging of MMP-2 expression in metastatic tumor models. *Int J Mol Sci.* 2014; 16:148–158. DOI: 10.3390/ijms16010148 [PubMed: 25547485]
198. Medina OP, Kairemo K, Valtanen H, Kangasniemi A, Kaukinen S, Ahonen I, Permi P, Annala A, Sneek M, Holopainen JM, Karonen SL, Kinnunen PKJ, Koivunen E. Radionuclide imaging of tumor xenografts in mice using a gelatinase-targeting peptide. *Anticancer Res.* 2005; 25:33–42. [PubMed: 15816516]
199. Penate Medina O, Haikola M, Tahtinen M, Simpura I, Kaukinen S, Valtanen H, Zhu Y, Kuosmanen S, Cao W, Reunanen J, Nurminen T, Saris PEJ, Smith-Jones P, Bradbury M, Larson S, Kairemo K. Liposomal Tumor Targeting in Drug Delivery Utilizing MMP-2- and MMP-9-

Binding Ligands. *J Drug Deliv.* 2011; 2011:160515.doi: 10.1155/2011/160515 [PubMed: 21490745]

200. Zou Y, Chen Y, Jiang Y, Gao J, Gu J. Targeting matrix metalloproteinases and endothelial cells with a fusion peptide against tumor. *Cancer Res.* 2007; 67:7295–7300. DOI: 10.1158/0008-5472.CAN-06-3920 [PubMed: 17671198]
201. Wang H, Yang Z, Gu J. Therapeutic targeting of angiogenesis with a recombinant CTT peptide-endostatin mimic-kringle 5 protein. *Mol Cancer Ther.* 2014; 13:2674–2687. DOI: 10.1158/1535-7163.MCT-14-0266 [PubMed: 25127900]
202. Xu J, Liu X, Li L, Zhang S, Li Y, Gao R. An engineered TIMP2-based and enediyne-integrated fusion protein for targeting MMP-14 shows potent antitumor efficacy. *Oncotarget.* 2015; 6:26322–26334. [PubMed: 26314845]
203. Mishiro K, Ishiguro M, Suzuki Y, Tsuruma K, Shimazawa M, Hara H. A broad-spectrum matrix metalloproteinase inhibitor prevents hemorrhagic complications induced by tissue plasminogen activator in mice. *Neuroscience.* 2012; 205:39–48. DOI: 10.1016/j.neuroscience.2011.12.042 [PubMed: 22244977]
204. Renkiewicz R, Qiu L, Lesch C, Sun X, Devalaraja R, Cody T, Kaldjian E, Welgus H, Baragi V. Broad-spectrum matrix metalloproteinase inhibitor marimastat-induced musculoskeletal side effects in rats. *Arthritis Rheum.* 2003; 48:1742–1749. DOI: 10.1002/art.11030 [PubMed: 12794843]
205. Zucker S, Cao J. Selective matrix metalloproteinase (MMP) inhibitors in cancer therapy: ready for prime time? *Cancer Biol Ther.* 2009; 8:2371–2373. [PubMed: 19959934]
206. Fingleton B. MMPs as therapeutic targets - still a viable option? *Semin Cell Dev Biol.* 2009; 19:61–68. DOI: 10.1016/j.semcdb.2007.06.006.MMPs
207. Giersing BK, Rae MT, Carballido-Brea M, Williamson RA, Blower PJ. Synthesis and characterization of ¹¹¹In-DTPA-N-TIMP-2: a radiopharmaceutical for imaging matrix metalloproteinase expression. *Bioconjug Chem.* 2001; 12:964–971. doi:10.1021%2Fbc010028f. [PubMed: 11716687]
208. Kulasegaram R, Giersing B, Page CJ, Blower PJ, Williamson RA, Peters BS, O'Doherty MJ. In vivo evaluation of ¹¹¹In-DTPA-N-TIMP-2 in Kaposi sarcoma associated with HIV infection. *Eur J Nucl Med.* 2001; 28:756–761.
209. Orian-Rousseau V. CD44, a therapeutic target for metastasising tumours. *Eur J Cancer.* 2010; 46:1271–1277. DOI: 10.1016/j.ejca.2010.02.024 [PubMed: 20303742]
210. Rogers, CE., Williams, S. *HER2 and Cancer: Mechanism, Testing, and Targeted Therapy.* Nova Science Publishers, Inc; 2011.
211. Zhu L, Kate P, Torchilin VP. Matrix metalloprotease 2-responsive multifunctional liposomal nanocarrier for enhanced tumor targeting. *ACS Nano.* 2012; 6:3491–3498. DOI: 10.1021/nn300524f [PubMed: 22409425]
212. Perche F, Torchilin VP. Recent trends in multifunctional liposomal nanocarriers for enhanced tumor targeting. *J Drug Deliv.* 2013; 2013:705265.doi: 10.1155/2013/705265 [PubMed: 23533772]
213. Jenkins MH, Alrowaished SS, Goody MF, Crawford BD, Henry CA. Laminin and Matrix metalloproteinase 11 regulate Fibronectin levels in the zebrafish myotendinous junction. *Skelet Muscle.* 2016; 6:18.doi: 10.1186/s13395-016-0089-3 [PubMed: 27141287]
214. Erler JT, Bennewith KL, Nicolau M, Dornhöfer N, Kong C, Le Q-T, Chi J-TA, Jeffrey SS, Giaccia AJ. Lysyl oxidase is essential for hypoxia-induced metastasis. *Nature.* 2006; 440:1222–6. DOI: 10.1038/nature04695 [PubMed: 16642001]
215. Culhaci N, Metin K, Copcu E, Dikicioglu E. Elevated expression of MMP-13 and TIMP-1 in head and neck squamous cell carcinomas may reflect increased tumor invasiveness. *BMC Cancer.* 2004; 4:42.doi: 10.1186/1471-2407-4-42 [PubMed: 15291964]
216. Wu W, Billingham RC, Pidoux I, Antoniou J, Zukor D, Tanzer M, Poole AR. Sites of collagenase cleavage and denaturation of type II collagen in aging and osteoarthritic articular cartilage and their relationship to the distribution of matrix metalloproteinase 1 and matrix metalloproteinase 13. *Arthritis Rheum.* 2002; 46:2087–2094. DOI: 10.1002/art.10428 [PubMed: 12209513]

217. Zhou Z, Qutaish M, Han Z, Schur RM, Liu Y, Wilson DL, Lu Z. MRI detection of breast cancer micrometastases with a fibronectin-targeting contrast agent. *Nat Commun.* 2015; 6:7984.doi: 10.1038/ncomms8984 [PubMed: 26264658]
218. Wuest M, Kuchar M, Sharma SK, Richter S, Hamann I, Wang M, Vos L, Mackey JR, Wuest F, Löser R. Targeting lysyl oxidase for molecular imaging in breast cancer. *Breast Cancer Res.* 2015; 17:107.doi: 10.1186/s13058-015-0609-9 [PubMed: 26265048]
219. Sorensen IV. Characterization of Anti-TIMP-1 Monoclonal Antibodies for Immunohistochemical Localization in Formalin-fixed, Paraffin-embedded Tissue. *J Histochem Cytochem.* 2006; 54:1075–1086. DOI: 10.1369/jhc.5A6896.2006 [PubMed: 16517973]
220. Li Y, Yu M. Targeting and mimicking collagens via triple helical peptide assembly. *Curr Opin Chem Biol.* 2013; 17doi: 10.1016/j.cbpa.2013.10.018
221. Wahyudi H, Reynolds AA, Li Y, Owen SC, Yu SM. Targeting collagen for diagnostic imaging and therapeutic delivery. *J Control Release.* 2016; 240:323–331. DOI: 10.1016/j.jconrel.2016.01.007 [PubMed: 26773768]
222. Yang X, Iyer AK, Singh A, Choy E, Hornicek FJ, Amiji MM, Duan Z. MDR1 siRNA loaded hyaluronic acid-based CD44 targeted nanoparticle systems circumvent paclitaxel resistance in ovarian cancer. *Sci Rep.* 2015; 5:8509.doi: 10.1038/srep08509 [PubMed: 25687880]
223. Alam M, Mohammad A, Rahman S, Todd K, Shuaib A. Hyperthermia up-regulates matrix metalloproteinases and accelerates basement membrane degradation in experimental stroke. *Neurosci Lett.* 2011; 495:135–139. DOI: 10.1016/j.neulet.2011.03.056 [PubMed: 21443925]
224. Fang JY, Tan S-J, Wu Y-C, Yang Z, Hoang BX, Han B. From competency to dormancy: a 3D model to study cancer cells and drug responsiveness. *J Transl Med.* 2016; 14:38.doi: 10.1186/s12967-016-0798-8 [PubMed: 26847768]
225. Nanni SB, Pratt J, Beauchemin D, Haidara K, Annabi B. Impact of Concanavalin-A-Mediated Cytoskeleton Disruption on Low-Density Lipoprotein Receptor- Related Protein-1 Internalization and Cell Surface Expression in Glioblastomas. *Biomark Cancer.* 2016; 8:77–87. DOI: 10.4137/BIC.S38894.TYPE [PubMed: 27226736]
226. Xiong J, Li Z, Zhang Y, Li D, Zhang G, Luo X, Jie Z, Liu Y, Cao Y, Le Z, Tan S, Zou W, Gong P, Qiu L, Li Y, Wang H, Chen H. PRL-3 promotes the peritoneal metastasis of gastric cancer through the PI3K/Akt signaling pathway by regulating PTEN. *Oncol Rep.* 2016; 36:1819–28. DOI: 10.3892/or.2016.5030 [PubMed: 27572739]
227. Tejima E, Zhao B-Q, Tsuji K, Rosell A, van Leyen K, Gonzalez RG, Montaner J, Wang X, Lo EH. Astrocytic induction of matrix metalloproteinase-9 and edema in brain hemorrhage. *J Cereb Blood Flow Metab.* 2007; 27:460–8. DOI: 10.1038/sj.jcbfm.9600354 [PubMed: 16788715]
228. Fingleton B, Vargo-Gogola T, Crawford HC, Matrisian LM. Matrilysin [MMP-7] expression selects for cells with reduced sensitivity to apoptosis. *Neoplasia.* 2001; 3:459–68. DOI: 10.1038/sj/neo/7900190 [PubMed: 11774028]
229. Mitsiades N, Yu WH, Poulaki V, Tsokos M, Stamenkovic I. Matrix metalloproteinase-7-mediated cleavage of Fas ligand protects tumor cells from chemotherapeutic drug cytotoxicity. *Cancer Res.* 2001; 61:577–581. [PubMed: 11212252]
230. Liu H, Zhang T, Wu B, Huang J, Zhou Y, Zhu J. Chronic exposure to exogenous matrilysin induces chemoresistance and enhances Bcl-2 expression in A549 lung adenocarcinoma cells. *Mol Biol Rep.* 2009; 36:2099.doi: 10.1007/s11033-008-9422-1 [PubMed: 19107575]
231. Huang Y, Yu H, Lei H, Xie C, Zhong Y. Matrix metalloproteinase 7 is a useful marker for 5-fluorouracil-based adjuvant chemotherapy in stage II and stage III colorectal cancer patients. *Med Oncol.* 2014; 31:824.doi: 10.1007/s12032-013-0824-0 [PubMed: 24469951]
232. Almendro V, Ametller E, García-Recio S, Collaza O, Casas I, Augé JM, Maurel J, Gascón P. The role of MMP7 and its cross-talk with the FAS/FASL system during the acquisition of chemoresistance to oxaliplatin. *PLoS One.* 2009; 4:e4728.doi: 10.1371/journal.pone.0004728 [PubMed: 19266094]
233. Cheng-Keng C, Pang S-T, Chuang T-J, Liao S-K. Profiling of matrix metalloproteinases and tissue inhibitors of metalloproteinases proteins in bladder urothelial carcinoma. *Oncol Lett.* 2010; 1:691–695. DOI: 10.3892/ol [PubMed: 22966365]

234. Wallard MJ, Pennington CJ, Veerakumarasivam A, Burt G, Mills IG, Warren A, Leung HY, Murphy G, Edwards DR, Neal DE, Kelly JD. Comprehensive profiling and localisation of the matrix metalloproteinases in urothelial carcinoma. *Br J Cancer*. 2006; 94:569–577. DOI: 10.1038/sj.bjc.6602931 [PubMed: 16465195]
235. Shiomi T, Okada Y. MT1-MMP and MMP-7 in invasion and metastasis of human cancers. *Cancer Metastasis Rev*. 2003; 22:145–152. DOI: 10.1023/A:1023039230052 [PubMed: 12784993]
236. Boström P, Söderström M, Vahlberg T, Söderström K-O, Roberts PJ, Carpén O, Hirsimäki P. MMP-1 expression has an independent prognostic value in breast cancer. *BMC Cancer*. 2011; 11:1–8. DOI: 10.1186/1471-2407-11-348 [PubMed: 21194487]
237. Köhrmann A, Kammerer U, Kapp M, Dietl J, Anacker J. Expression of matrix metalloproteinases (MMPs) in primary human breast cancer and breast cancer cell lines: New findings and review of the literature. *BMC Cancer*. 2009; 9:188.doi: 10.1186/1471-2407-9-188 [PubMed: 19531263]
238. Benson CS, Babu SD, Radhakrishna S, Selvamurugan N, Sankar BR. Expression of matrix metalloproteinases in human breast cancer tissues. *Dis Markers*. 2013; 34:395–405. DOI: 10.3233/DMA-130986 [PubMed: 23568046]
239. Asano T, Tada M, Cheng S, Takemoto N, Kuramae T, Abe M, Takahashi O, Miyamoto M, Hamada JI, Moriuchi T, Kondo S. Prognostic Values of Matrix Metalloproteinase Family Expression in Human Colorectal Carcinoma. *J Surg Res*. 2008; 146:32–42. DOI: 10.1016/j.jss.2007.02.011 [PubMed: 17543340]
240. Baker EA, Bergin FG, Leaper DJ. Matrix metalloproteinases, their tissue inhibitors and colorectal cancer staging. *Br J Surg*. 2000; 87:1215–1221. DOI: 10.1046/j.1365-2168.2000.01531.x [PubMed: 10971431]
241. Baker EA, Leaper DJ. The plasminogen activator and matrix metalloproteinase systems in colorectal cancer: Relationship to tumour pathology. *Eur J Cancer*. 2003; 39:981–988. DOI: 10.1016/S0959-8049(03)00065-0 [PubMed: 12706368]
242. Murray GI, Duncan ME, Arbuckle E, Melvin WT, Fothergill JE. Matrix metalloproteinases and their inhibitors in gastric cancer. *Gut*. 1998; 43:791–797. DOI: 10.1136/gut.43.6.791 [PubMed: 9824606]
243. Pyeon D, Newton MA, Lambert PF, Den Boon JA, Marsit CJ, Woodworth CD, Connor JP, Thomas H, Smith EM, Kelsey KT, Turek LP, Ahlquist P. Fundamental Differences in Cell Cycle Deregulation in Human Papillomavirus–Positive and Human Papillomavirus–Negative Head/Neck and Cervical Cancers. *Cancer Res*. 2007; 67:4605–4619. DOI: 10.1158/0008-5472.CAN-06-3619.Fundamental [PubMed: 17510386]
244. Ye H, Yu T, Temam S, Ziober BL, Wang J, Schwartz JL, Mao L, Wong DT, Zhou X. Transcriptomic dissection of tongue squamous cell carcinoma. *BMC Genomics*. 2008; 9:69.doi: 10.1186/1471-2164-9-69 [PubMed: 18254958]
245. Iizuka S, Ishimaru N, Kudo Y. Matrix Metalloproteinases: The Gene Expression Signatures of Head and Neck Cancer Progression. *Cancers (Basel)*. 2014; 6:396–415. DOI: 10.3390/cancers6010396 [PubMed: 24531055]
246. O-charoenrat P, Rhys-Evans PH, Eccles SA. Expression of matrix metalloproteinases and their inhibitors correlates with invasion and metastasis in squamous cell carcinoma of the head and neck. *Arch Otolaryngol Head Neck Surg*. 2001; 127:813–20. [PubMed: 11448356]
247. Pietruszewska W, Bojanowska-Pozniak K, Kobos J. Matrix metalloproteinases MMP1, MMP2, MMP9 and their tissue inhibitors TIMP1, TIMP2, TIMP3 in head and neck cancer : an immunohistochemical study. *Otolaryngol Pol*. 2016; 70:32–43. DOI: 10.5604/00306657.1202546 [PubMed: 27386931]
248. Schütz A, Schneidenbach D, Aust G, Tannapfel A, Steinert M, Wittekind C. Differential expression and activity status of MMP-1, MMP-2 and MMP-9 in tumor and stromal cells of squamous cell carcinomas of the lung. *Tumor Biol*. 2002; 23:179–184. DOI: 10.1159/000064034
249. Michael M, Babic B, Khokha R, Tsao M, Ho J, Pintilie M, Leco K, Chamberlain D, Shepherd FA. Expression and prognostic significance of metalloproteinases and their tissue inhibitors in patients with small-cell lung cancer. *J Clin Oncol*. 1999; 17:1802–8. <http://www.ncbi.nlm.nih.gov/pubmed/10561218>. [PubMed: 10561218]

250. Hofmann H-S, Hansen G, Richter G, Taege C, Simm A, Silber R-E, Burdach S. Matrix Metalloproteinase-12 Expression Correlates with Local Recurrence and Metastatic Disease in Non-Small Cell Lung Cancer Patients. *Clin Cancer Res.* 2005; 11:1086–1092. <http://clincancerres.aacrjournals.org/content/11/3/1086.short>. [PubMed: 15709175]
251. Lin GG, Scott JG. Tumor and salivary matrix metalloproteinase levels are strong diagnostic markers of oral squamous cell carcinoma. *Cancer Epidemiol Biomarkers Prev.* 2011; 20:2628–2636. DOI: 10.1158/1055-9965 [PubMed: 21960692]
252. Baker EA, Leaper DJ, Hayter JP, Dickenson AJ. The matrix metalloproteinase system in oral squamous cell carcinoma. *Br J Oral Maxillofac Surg.* 2006; 44:482–486. DOI: 10.1016/j.bjoms.2005.10.005 [PubMed: 16338034]
253. Yamamoto H, Itoh F, Iku S, Adachi Y, Fukushima H, Sasaki S, Mukaiya M, Hirata K, Imai K. Expression of Matrix Metalloproteinases and Tissue Inhibitors of Metalloproteinases in Human Pancreatic Adenocarcinomas: Clinicopathologic and Prognostic Significance of Matrilysin Expression. *J Clin Oncol.* 2001; 19:1118–1127. [PubMed: 11181677]
254. Jones LE, Humphreys MJ, Campbell F, Neoptolemos JP, Boyd MT. Comprehensive analysis of matrix metalloproteinase and tissue inhibitor expression in pancreatic cancer: increased expression of matrix metalloproteinase-7 predicts poor survival. *Clin Cancer Res.* 2004; 10:2832–45. DOI: 10.1158/1078-0432.ccr-1157-03 [PubMed: 15102692]
255. Monhian N, Jewett BS, Baker SR, Varani J. Matrix metalloproteinase expression in normal skin associated with basal cell carcinoma and in distal skin from the same patients. *Arch Facial Plast Surg Off Publ Am Acad Facial Plast Reconstr Surgery Inc Int Fed Facial Plast Surg Soc.* 2015; 7:238–243. DOI: 10.1001/archfaci.7.4.238
256. Sawaya RE, Yamamoto M, Gokaslan ZL, Wang SW, Mohanam S, Fuller GN, McCutcheon IE, Stetler-Stevenson WG, Nicolson GL, Rao JS. Expression and localization of 72 kDa type IV collagenase (MMP-2) in human malignant gliomas in vivo. *Clin Exp Metastasis.* 1996; 14:35–42. DOI: 10.1007/BF00157684 [PubMed: 8521615]
257. Choe G, Park JK, Jouben-Steele L, Kremen TJ, Liao LM, Vinters HV, Cloughesy TF, Mischel PS. Active matrix metalloproteinase 9 expression is associated with primary glioblastoma subtype. *Clin Cancer Res.* 2002; 8:2894–2901. [PubMed: 12231534]
258. Nakada M, Nakamura H, Ikeda E, Fujimoto N, Yamashita J, Sato H, Seiki M, Okada Y. Expression and tissue localization of membrane-type 1, 2, and 3 matrix metalloproteinases in human astrocytic tumors. *Am J Pathol.* 1999; 154:417–28. DOI: 10.1016/S0002-9440(10)65288-1 [PubMed: 10027400]
259. Kim T-D, Song K-S, Li G, Choi H, Park H-D, Lim K, Hwang B-D, Yoon W-H. Activity and expression of urokinase-type plasminogen activator and matrix metalloproteinases in human colorectal cancer. *BMC Cancer.* 2006; 6:211. doi: 10.1186/1471-2407-6-211 [PubMed: 16916471]
260. Pesta M, Holubec L, Topolcan O, Cerna M, Rupert K, Sen LH, Treska V, Kormunda S, Elgrova L, Finek J, Cerny R. Quantitative estimation of matrix metalloproteinases 2 and 7 (MMP-2, MMP-7) and tissue inhibitors of matrix metalloproteinases 1 and 2 (TIMP-1, TIMP-2) in colorectal carcinoma tissue samples. *Anticancer Res.* 2005; 25:3387–3391. [PubMed: 16101153]
261. Cho YB, Lee WY, Song SY, Shin HJ, Yun SH, Chun HK. Matrix metalloproteinase-9 activity is associated with poor prognosis in T3-T4 node-negative colorectal cancer. *Hum Pathol.* 2007; 38:1603–1610. DOI: 10.1016/j.humpath.2007.03.018 [PubMed: 17669467]
262. Chan CC, Menges M, Orzechowski HD, Orendain N, Pistorius G, Feifel G, Zeitz M, Stallmach A. Increased matrix metalloproteinase 2 concentration and transcript expression in advanced colorectal carcinomas. *Int J Colorectal Dis.* 2001; 16:133–140. DOI: 10.1007/s003840100287 [PubMed: 11459286]
263. Papadopoulou S, Scorilas A, Arnogianaki N, Papapanayiotou B, Tzimogianni A, Agnantis N, Talieri M. Expression of gelatinase-A (MMP-2) in human colon cancer and normal colon mucosa. *Tumor Biol.* 2001; 22:383–389. DOI: 10.1159/000050641
264. Langers AMJ, Verspaget HW, Hawinkels LJAC, Kubben FJGM, van Duijn W, van der Reijden JJ, Hardwick JCH, Hommes DW, Sier CFM. MMP-2 and MMP-9 in normal mucosa are independently associated with outcome of colorectal cancer patients. *Br J Cancer.* 2012; 106:1495–8. DOI: 10.1038/bjc.2012.80 [PubMed: 22472880]

265. Langers, aMJ., Sier, CFM., Ja, L., Hawinkels, C., Kubben, FJGM., van Duijn, W., van der Reijden, JJ., Lamers, CBHW., Hommes, DW., Verspaget, HW. MMP-2 geno-phenotype is prognostic for colorectal cancer survival, whereas MMP-9 is not. *Br J Cancer*. 2008; 98:1820–3. DOI: 10.1038/sj.bjc.6604380 [PubMed: 18506186]
266. Paunovi I, Tati S. Immunohistochemical localization of matrix metalloproteinase-2 (MMP-2) in medullary thyroid carcinoma. *Arch Oncol*. 2000; 8:95–97.
267. Weng Y, Cai M, Zhu J, Geng J, Zhu K, Jin X, Ding W. Matrix metalloproteinase activity in early-stage lung cancer. *Onkologie*. 2013; 36:256–9. DOI: 10.1159/000350304 [PubMed: 23689219]
268. Singh RD, Haridas N, Patel JB, Shah FD, Shukla SN, Shah PM, Patel PS. Matrix metalloproteinases and their inhibitors: Correlation with invasion and metastasis in oral cancer. *Indian J Clin Biochem*. 2010; 25:250–259. DOI: 10.1007/s12291-010-0060-8 [PubMed: 21731196]
269. Monteiro-Amado F, Castro-Silva II, de Lima CJ, Soares FA, Kowalski LP, Granjeiro JM. Immunohistochemical evaluation of MMP-2, MMP-9 and CD31/microvascular density in squamous cell carcinomas of the floor of the mouth. *Braz Dent J*. 2013; 24:3–9. <http://www.ncbi.nlm.nih.gov/pubmed/23657405>. [PubMed: 23657405]
270. Vos MC, Bekers E. Differential Associations of MMP-2 and MMP-14 with Stromal Amounts and T lymphocyte Presence in Ovarian Cancer. *J Mol Genet Med*. 2016; 10:1–7. DOI: 10.4172/1747-0862.1000201
271. Kamat AA, Fletcher M, Gruman LM, Mueller P, Lopez A, Landen CN, Han L, Gershenson DM, Sood AK. The clinical relevance of stromal matrix metalloproteinase expression in ovarian cancer. *Clin Cancer Res*. 2006; 12:1707–1714. DOI: 10.1158/1078-0432.CCR-05-2338 [PubMed: 16551853]
272. Yokoyama M, Ochi K, Ichimura M, Mizushima T, Shinji T, Koide N, Tsurumi T, Hasuoka H, Harada M. Matrix metalloproteinase-2 in pancreatic juice for diagnosis in pancreatic cancer. *Pancreas*. 2002; 24:344–347. [PubMed: 11961486]
273. Ross JS, Kaur P, Sheehan CE, Fisher HaG, Kaufman Ra, Kallakury BVS. Prognostic significance of matrix metalloproteinase 2 and tissue inhibitor of metalloproteinase 2 expression in prostate cancer. *Mod Pathol*. 2003; 16:198–205. DOI: 10.1097/01.MP.0000056984.62360.6C [PubMed: 12640098]
274. Wang Y, Xu H, Ueda Y, Shimasaki M, Wang E. Activation ratio of MMP-2 and expression of MT1-MMP are correlated in thymic epithelial tumours. *Pathology*. 2007; 39:486–490. DOI: 10.1080/00313020701569964 [PubMed: 17886098]
275. Stadlmann S, Pollheimer J, Moser PL, Raggi A, Amberger A, Margreiter R, Offner FA, Mikuz G, Dirnhofer S, Moch H. Cytokine-regulated expression of collagenase-2 (MMP-8) is involved in the progression of ovarian cancer. *Eur J Cancer*. 2003; 39:2499–2505. DOI: 10.1016/j.ejca.2003.08.011 [PubMed: 14602136]
276. Polistena A, Cucina A, Dinicola S, Stene C, Cavallaro G, Ciardi A, Orlando G, Arena R, D'Ermo G, Cavallaro A, Johnson LB, De Toma G. MMP7 expression in colorectal tumours of different stages. *In Vivo (Brooklyn)*. 2014; 28:105–110.
277. Pryczynicz A, Gryko M, Niewiarowska K, Dymicka-Piekarska V, Ustymowicz M, Hawryluk M, Cepowicz D, Borsuk A, Kemonia A, Famulski W, Guzinska-Ustymowicz K. Immunohistochemical expression of MMP-7 protein and its serum level in colorectal cancer. *Folia Histochem Cytobiol*. 2013; 51:206–212. [PubMed: 24203626]
278. Keles D, Arslan B, Terzi C, Tekmen I, Dursun E, Altungoz O, Oktay G. Expression and activity levels of matrix metalloproteinase-7 and in situ localization of caseinolytic activity in colorectal cancer. *Clin Biochem*. 2014; 47:1265–1271. DOI: 10.1016/j.clinbiochem.2014.06.004 [PubMed: 24930385]
279. Liu D, Nakano J, Ishikawa S, Yokomise H, Ueno M, Kadota K, Urushihara M, Huang Clong. Overexpression of matrix metalloproteinase-7 (MMP-7) correlates with tumor proliferation, and a poor prognosis in non-small cell lung cancer. *Lung Cancer*. 2007; 58:384–391. DOI: 10.1016/j.lungcan.2007.07.005 [PubMed: 17728005]
280. Duffy M, Blaser J, Duggan C, McDermott E, O'Higgins N, Fennelly J, Tschesche H. Assay of matrix metalloproteinases types 8 and 9 by ELISA in human breast cancer. *Br J Cancer*. 1995; 71:1025–1028. [PubMed: 7734294]

281. Rao JS, Yamamoto M, Mohaman S, Gokaslan ZL, Fuller GN, Stetlerstevenson WG, Rao VH, Liotta La, Nicolson GL, Sawaya RE. Expression and Localization of 92 kDa Type-IV Collagenase Gelatinase-B (MMP-9) in Human Gliomas. *Clin Exp Metastasis*. 1996; 14:12–18. [PubMed: 8521611]
282. Wu Z-S, Wu Q, Yang J-H, Wang H-Q, Ding X-D, Yang F, Xu X-C. Prognostic significance of MMP-9 and TIMP-1 serum and tissue expression in breast cancer. *Int J Cancer*. 2008; 122:2050–2056. DOI: 10.1002/ijc.23337 [PubMed: 18172859]
283. Kim E-Y, Song H-Y, Kim JC, Yoon YS, Ye BD, Nam DH, Shin S-J. Mmp-9 expression after metallic stent placement in patients with colorectal cancer: association with in-stent restenosis. *Radiology*. 2014; 271:901–8. DOI: 10.1148/radiol.13121794 [PubMed: 24475847]
284. Marecko I, Cvejic D, Selemetjev S, Paskas S, Tatic S, Paunovic I, Savin S. Enhanced activation of matrix metalloproteinase-9 correlates with the degree of papillary thyroid carcinoma infiltration. *Croat Med J*. 2014; 55:128–37. DOI: 10.3325/cmj.2014.55.128 [PubMed: 24778099]
285. Sun L, Diamond ME, Ottaviano AJ, Joseph MJ, Ananthanarayan V, Munshi HG. Transforming growth factor-beta 1 promotes matrix metalloproteinase-9-mediated oral cancer invasion through snail expression. *Mol Cancer Res*. 2008; 6:10–20. DOI: 10.1158/1541-7786.MCR-07-0208 [PubMed: 18234959]
286. Tian M, Cui Y-Z, Song G-H, Zong M-J, Zhou X-Y, Chen Y, Han J-X. Proteomic analysis identifies MMP-9, DJ-1 and A1BG as overexpressed proteins in pancreatic juice from pancreatic ductal adenocarcinoma patients. *BMC Cancer*. 2008; 8:241.doi: 10.1186/1471-2407-8-241 [PubMed: 18706098]
287. Deraz EM, Kudo Y, Yoshida M, Obayashi M, Tsunematsu T, Tani H, Siriwardena SBSM, Kiekhade MR, Qi G, Iizuka S, Ogawa I, Campisi G, Lo Muzio L, Abiko Y, Kikuchi A, Takata T. MMP-10/stromelysin-2 promotes invasion of head and neck cancer. *PLoS One*. 2011; 6doi: 10.1371/journal.pone.0025438
288. Justilien V, Regala RP, Tseng IC, Walsh MP, Batra J, Radisky ES, Murray NR, Fields AP. Matrix metalloproteinase-10 is required for lung cancer stem cell maintenance, tumor initiation and metastatic potential. *PLoS One*. 2012; 7:1–12. DOI: 10.1371/journal.pone.0035040
289. Suomela S, Koljonen V, Skoog T, Kukko H, Bohling T, Saarialho-Kere U. Expression of MMP-10, MMP-21, MMP-26, and MMP-28 in Merkel cell carcinoma. *Virchows Arch*. 2009; 455:495. doi:10.1007. [PubMed: 19921252]
290. Peruzzi D, Mori F, Conforti A, Lazzaro D, De Rinaldis E, Ciliberto G, La Monica N, Aurisicchio L. MMP11: A novel target antigen for cancer immunotherapy. *Clin Cancer Res*. 2009; 15:4104–4113. DOI: 10.1158/1078-0432.CCR-08-3226 [PubMed: 19509157]
291. Leeman MF, McKay JA, Murray GI. Matrix metalloproteinase-13 activity is associated with poor prognosis in colorectal cancer. *J Clin Pathol*. 2002; 55:758–762. [PubMed: 12354802]
292. Etoh T, Inoue H, Yoshikawa Y, Barnard GF, Kitano S, Mori M. Increased expression of collagenase-3 (MMP-13) and MT1-MMP in oesophageal cancer is related to cancer aggressiveness. *Gut*. 2000; 47:50–56. DOI: 10.1136/gut.47.1.50 [PubMed: 10861264]
293. Nuttall RK, Pennington CJ, Taplin J, Wheal A, Yong VW, Forsyth Pa, Edwards DR. Elevated membrane-type matrix metalloproteinases in gliomas revealed by profiling proteases and inhibitors in human cancer cells. *Mol Cancer Res*. 2003; 1:333–45. <http://www.ncbi.nlm.nih.gov/pubmed/12651907>. [PubMed: 12651907]
294. Atkinson JM, Pennington CJ, Martin SW, Anikin VA, Mearns AJ, Loadman PM, Edwards DR, Gill JH. Membrane type matrix metalloproteinases (MMPs) show differential expression in non-small cell lung cancer (NSCLC) compared to normal lung: Correlation of MMP-14 mRNA expression and proteolytic activity. *Eur J Cancer*. 2007; 43:1764–1771. DOI: 10.1016/j.ejca.2007.05.009 [PubMed: 17600697]
295. Jian P, Yanfang T, Zhuan Z, Jian W, Xueming Z, Jian N. MMP28 (epilysin) as a novel promoter of invasion and metastasis in gastric cancer. *BMC Cancer*. 2011; 11:200.doi: 10.1186/1471-2407-11-200 [PubMed: 21615884]

Figure 1.

Correlation between MMP (all subtypes) expression and cancer stage (all cancer types) obtained through analysis of 70 different published human cancer tissue evaluations. Each data point represents a complete study where an average cancer stage was calculated or subset of a larger study with defined cancer stages for evaluation. Cancer stages of 0 are adenomas and are not healthy tissue. (a) Percent tissue expression of all particular MMP subtypes vs. cancer stage, (b) Genetic expression (fold-change over healthy complementary tissue) vs. cancer stage, (c) Protein expression (fold-change over healthy complementary tissue) vs. cancer stage, and (d) MMP activity levels (fold-change over healthy complementary tissue) vs. cancer stage. Complete methods are included in Methods S2.

Figure 2. Active MMP subtype distribution in a generalized cancer cell and locations of highest expression in primary tumors. Only statistically-significant differences in tumor region expression levels are shown. MMP-1, MMP-7, MMP-14, and MMP-19 showed statistical significance in favoring of both the tumor center and the invasive front in conflicting studies; in this case, the greater statistical-significance is represented.

Figure 3.
Types of drug delivery systems developed upon MMP-responsive principles.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Table 1

MMP concentrations and genetic, protein, and activity levels of upregulation in cancers

MMP	Cancer Type	Healthy Tissue Expression (%)	Cancer Tissue Expression (%)	Genetic Upregulation (Fold-Change)	Healthy Tissue Concentration (ng/mg)	Cancer Tissue Concentration (ng/mg)	Protein Expression Upregulation (Fold-Change)	Activity Upregulation (Fold-Change)	References
MMP-1	Bladder		100	8.57					[233,234]
	Brain				0	0	0		[235]
	Breast	13.3	77.5	9.6	0.5	1.6	5.41		[78,235–238]
	Colorectal			5.33	0.17	9.79	56.59		[239–241]
	Gastrointestinal		73		2.6	3.1	0.19		[235,242]
	Head and Neck		63.8	79.6					[243–247]
	Lung	47.3	58.6	2.67					[248–250]
	Oral			218.4	1.2	31.6	25.3		[235,251,252]
	Pancreatic		65.4						[253,254]
	Thyroid	30			0	0	0		[235]
MMP-2	Skin								[255]
	Metastases [†]			3.5					[246]
	All Cancers	30.2	73.05	46.81	0.75	7.68	21.87		
	Bladder		63.3	6.97					[233,234]
	Brain	0	20	5.1	71.89	155.37	1.16	4.6	[235,256–258]
	Breast			0.58	2.9	17.08	3.32	0.25	[81,82,235,237,238]
	Colorectal	65	92	0.38	4.9	24.55	4.01	4.79	[95,239–241,259–265]
	Gastrointestinal		94.6		17.3	25.2	0.46		[235,242]
	Head and Neck		25.4	1.19					[243–247,266]
	Lung	8.6	4.4	0.02				0.52	[248–250,267]
	Oral		53.7	1.84	3.79	10.29	1.72		[235,251,252,268,269]
	Ovarian		71.5						[270,271]
	Pancreatic	58.8	75.9						[253,254,272]
	Prostate		76.1						[273]
	Skin							0.09	[255]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

MMP Cancer Type	Healthy Tissue Expression (%)	Cancer Tissue Expression (%)	Genetic Upregulation (Fold-Change)	Healthy Tissue Concentration (ng/mg)	Cancer Tissue Concentration (ng/mg)	Protein Expression Upregulation (Fold-Change)	Activity Upregulation (Fold-Change)	References
Thymus	25	87.5	101.23					[274]
Thyroid				2.9	10.1	2.48		[235]
Metastases [†]			3.2		2.42	0.42		[246,258,262]
All Cancers	31.48	60.4	13.39	17.28	35.0	1.94	2.05	
MMP-3								
Bladder		6.7						[233]
Brain				0	0.5	>10		[235]
Breast			0.28	1.6	9.7	6.01		[235,237,238]
Colorectal			8.5	1.1	3.99	2.63		[239–241]
Gastrointestinal		27		2.7	2.7	0		[235,242]
Head and Neck			20.05					[243–246]
Lung		21.7	0.08					[249,250]
Oral			39.3	3.28	9.13	1.78		[235,251,252]
Ovarian		2.6						[275]
Pancreatic	100	76.37						[253,254]
Thyroid				1.6	2.2	0.38		[235]
Metastases [†]			2.00					[246]
All Cancers	100	14.5	11.70	1.85	3.695	3.03		
MMP-7								
Brain				0	0	0		[235]
Breast			-6.9	0	0	1.29		[235,237,238]
Colorectal	17	77.4	23.75	0.00	2.45	>200		[239,260,276–278]
Gastrointestinal				0.6	0.6	0		[235]
Head and Neck			2.69					[243–246]
Lung		48.3						[250,279]
Oral				0	0	0		[235]
Ovarian		81.8						[275]
Pancreatic	20	91.1		23	143	5.22		[89,254]
Thyroid				0	0	0		[235]
Metastases [†]			0.7					[246]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

MMP Cancer Type	Healthy Tissue Expression (%)	Cancer Tissue Expression (%)	Genetic Upregulation (Fold-Change)	Healthy Tissue Concentration (ng/mg)	Cancer Tissue Concentration (ng/mg)	Protein Expression Upregulation (Fold-Change)	Activity Upregulation (Fold-Change)	References
All Cancers	18.5	74.65	5.06	3.4	20.9	51.6		
MMP-8								
Brain				1.3	3.9	2.0		[235]
Breast			3.02	0.7	6.08	0.71		[235,237,238,280]
Colorectal			0.80					[239]
Gastrointestinal				29.9	42.3	0.41		[235]
Head and Neck			0.01					[244]
Lung			0.22					[250]
Oral				10.4	65.7	5.32		[235]
Ovarian		94.8						[275]
Pancreatic	60	73.3						[254]
Thyroid				4.6	3.3	-0.39		[235]
All Cancers	60	84.05	1.01	9.4	24.3	1.61		
MMP-9								
Bladder		70						[233]
Brain	4.3	74.5	9.2	76.97	1957.2	25.43		[235,257,281]
Breast		76.8	4.36	1.8	32.27	2.07	0.18	[82,235,237,238,280,282]
Colorectal	77.3	62.4	7.33	3.84	83.49	20.74	121.13	[95,239-241,259,261,264,265,283]
Gastrointestinal		72.6		15.6	32.2	1.06		[235,242]
Head and Neck	13.5	49.9	4.94					[243-247,284]
Lung	40.3	69.4	0.55				-0.32	[248-250,267]
Oral	50	67.1	5.45	4.26	11.16	1.62		[235,251,252,268,269,285]
Ovarian		66.8						[275]
Pancreatic		66.3						[253,254,286]
Skin							2.75	[255]
Thyroid				4.6	5.5	0.20		[235]
Metastases [‡]			1.5					[284]
All Cancers	37.08	67.58	4.76	17.85	353.64	8.52	30.44	

^{*} Both mean and median values were utilized in calculations

[‡] Metastases were not distinguished by resident tissue or by primary tumor type