Matrix Metalloproteinases and Breast Cancer

Soraiya Ebrahimpour Koujan,[1] Bahram Pourghassem Gargarib,[2,*] and Mohammad Khalili[3]

[1]Students Research Committee, Department of Biochemistry and Diet Therapy, Faculty of Nutrition, Tabriz University of Medical Sciences, Tabriz, IR Iran
[2]Nutrition Research Center, Department of Biochemistry and Diet Therapy, Faculty of Nutrition, Tabriz University of Medical Sciences, Tabriz, IR Iran
[3]Neuroscience Research Center, Tabriz University of Medical Sciences, Tabriz, IR Iran

Corresponding author: Bahram Pourghassem Gargarib, Nutrition Research Center, Department of Biochemistry and Diet Therapy, Faculty of Nutrition, Tabriz University of Medical Sciences, Tabriz, IR Iran. Tel: +98-4113357580, E-mail: bahrampg@yahoo.com

Abstract
Context: Matrix metalloproteinases (MMPs) are multigene family structurally and functionally related endoproteinases. The basic action of 23 types of MMPs collectively involves degradation of virtually every component of extracellular matrix (ECM) in tumor cells migration and metastasis process. This review article aimed at surveying MMPs specific role in various steps and cellular pathways involving in breast carcinogenesis.
Evidence Acquisition: This review article compromised published articles in PubMed and GoogleScholar according to keywords since 1988.
Results: Based on the recent researches, certain MMPs play critical role in breast cancer initiation, invasion, and metastasis. They can be regarded as predictive biomarkers of primary diagnosis and prognosis of breast cancer and have predictive value for evaluation of disease, tumor recurrence, invading of tumor cells to other sites and therapeutic outcomes.
Conclusions: In summary, the results of this review article provide rational evidences for applying in human clinical trials toward MMPs in breast cancer therapies.

Keywords: Matrix; Breast Cancer; Metastasis

1. Context

MMPs (matrix metalloproteinases) known as matrixins are zinc dependent enzymes, that are a multigene family structurally and functionally related endoproteinases (1, 2). Their basic mechanism of action collectively involves degradation of virtually every component of extracellular matrix (ECM) such as collagen, gelatin, fibronectin, vitronectin, and laminin (2, 3). There are 23 types of human MMPs, including 17 soluble secreted and 6 membrane type enzymes (Table 1) (4). MMPs have been described as enzymes, which are specific in their domain structure, have their particular substrate and expression patterns (4). MMPs are originally divided into subgroups based on their preferred substrates within extracellular matrix: collagenases (MMP-1, -8, -13), gelatinases (MMP-2, -9), stromelysins (MMP-3, -10, -11), matrilysins (MMP-7), and membrane-associated MMPs, including MT1-MMP/MMP-14, -15, -16, -17, -24, -25(4, 5). Breast cancer is the most common cause of death among women. Its incidence rate is very high in western communities as well as Iranian women. Despite advanced therapies such as surgery, radiotherapy, and chemotherapy, its prognosis remains poor and multi-target therapies are essential in order to overcoming the metastasis. Therefore, understanding and explanation of possible mechanism involving in the breast carcinogenesis are necessary (6). The purpose of this review article is surveying the MMPs specific role in various steps of breast carcinogenesis, including initiation, progression and metastasis, and cellular pathways involving in breast cancer metastasis.

2. Evidence Acquisition

This review article comprised published articles in PubMed and GoogleScholar since 1988. The articles were searched according to the Mesh terms of keywords including "breast" AND "neoplasm" AND "matrix metalloproteinase" in PubMed and GoogleScholar data bases. A total of 129 articles were obtained in primary search and surveyed based on inclusion and exclusion criteria. Inclusion criteria of this study were breast carcinogenesis, breast cancer, metastasis, and matrix metalloproteinase. Exclusion criteria were other cancers such as colon, prostate, gastric, ovarian, brain, and so on. Eighty-seven articles met the inclusion criteria and the context of the articles was considered.

Table 1. MMPs Types and Their Structural Class (4) [a]

MMP Designation	Structural Class
MMP-1	Simple hemopexin domain
MMP-2	Gelatin binding
MMP-3	Simple hemopexin domain
MMP-7	Minimal domain
MMP-8	Simple hemopexin domain
MMP-9	Gelatin binding
MMP-10	Simple hemopexin domain
MMP-11	Furin-activated and secreted
MMP-12	Simple hemopexin domain
MMP-13	Simple hemopexin domain
MMP-14	Transmembrane
MMP-15	Transmembrane
MMP-16	Transmembrane
MMP-17	GPI linked
MMP-18	Simple hemopexin domain
MMP-19	Simple hemopexin domain
MMP-20	Simple hemopexin domain
MMP-21	Vitronectin-like insert
MMP-22	Simple hemopexin domain
MMP-23	Type 2 transmembrane
MMP-24	Transmembrane
MMP-25	GPI linked
MMP-26	Minimal domain
MMP-27	Simple hemopexin domain
MMP-28	Furin-activated and secreted
No designation	Simple hemopexin domain
No designation	Simple hemopexin domain
No designation	Gelatin binding

[a] Abbreviations: MMP: Matrix Metalloproteinase.

3. Results

3.1. Catalytic Activity of MMPs

MMPs are catalytic enzymes, which are synthesized as inactive prozymogenes. Catalytic activity depends on the zinc ions at the catalytic active site. Interaction between a cysteine-sulphydryl group in propeptide domain and zinc ion bound to the catalytic domain, keeps them inactive. They are activated by proteinase activity on prodomain that depend on the presence of the zinc ion at the catalytic active site (1, 5, 7). Activation of MMPs usually occurs outside the cells by other activated MMPs or serine proteinase. But MMP-11, MMP-28, and MT-MMPs can also be activated by intracellular furin-like serine proteinase before being localized at the cell surface (7). Observations from mammary glands-epithelial cells have demonstrated some interaction among PEX domains and integrins or other cell surface receptors, which might mediate MMP activation; This process recruits soluble MMP in specific site of proteolysis in extracellular matrix (ECM) or regulates MMP endocytosis and turnover (8). In an experimental murin mammary carcinoma model, binding of MMP-9 to the hyaluronan receptor CD44 mediated catalytic activation of transforming growth factor-β (TGF-β) and resulted in tumor progression and angiogenesis (9). Membrane type-1 MMP (MT1-MMP) PEX domain docking to CD44 leads to localization of MT1-MMP at the leading edge of migration cells and facilities their migration (10, 11).

3.2. Polymorphism of MMPs in Breast Cancer

Breast cancer is the most common female cancer in the world. Although a high rate of breast cancer has been seen in Western communities, there is a dramatic increase in breast cancer incidence among Iranian women as well (6). Based on numerous clinical and epidemiological studies, certain MMPs and ADAMS play a major role in breast cancer. They can be regarded as predictive biomarkers of primary diagnosis and prognosis of breast cancer and have predictive value for evaluation of disease, tumor recurrence, invading of tumor cells to other sites, and therapeutic outcomes (2). A systematic review that was carried out on MMP-1, -2, -3, -9 polymorphisms in breast cancer concluded that there is no significance association between polymorphism of MMP-1, -2, -3, -9 and breast cancer (12).

3.3. Role of MMPs in Initiation of Breast Cancer

Although MMPs roles were regarded as exclusively significant in promotion, invasion, and metastasis of cancer cells, recent evidence suggests that MMPs participate in several stages of cancer progression altering 6 principle processes of cell physiology, including self-supporting growth signals, resistance to growth inhibitory signals, insensitivity to apoptosis, over replication, angiogenesis, and invasion to other tissues and metastasis (5, 13).

MMPs are normally secreted by two major sources cancerous cells, which produce MMP-7 and tumor stromal cells, which secrete MMP-2 and MMP-9. MMPs of the second group are ultimately recruited to cancer cell membranes. In fact, MMP-2 is produced by stromal cells of breast tumor while MMP-9 is found in both stromal and cancer cell membranes (5). It is noteworthy that upregulation of MMPs in breast cancer is not a result of gene amplification or mutations. Perhaps increase in MMP expression is due to transcriptional changes rather than loss of genes that encoding the MMPs mRNA. So this state probably results from mutations on oncogene or tumor suppressors that leads to activation of oncogenes and disruption of tumor suppressors (5). Most common genetic mutations that contribute to breast cancer include c-oncogenes such as C-erbB-2, C-myc, Ras, and tumor

suppressor genes such as p53 and RB. A mutation in p53 results in upregulation of all downstream classical oncogenes and transcription of MMP-1 and MMP-13 (1, 14, 15). However, some of c-oncogenes by modulating expression of MMPs contribute to tumorigenesis. For example, transfection of C-erbB-2 or C-Ras to non-invasive MCF-7, breast cancer cell lines, which leads to upregulation of MMP-2 expression (16). Whereas, transfection of PEA-3 to MCF-7 cells results in MMP-9 overproduction (17).

3.4. MMPs and Breast Cancer Cell Growth

Animal studies carried out about MMPs roles in breast cancer have clarified that overexpression of WAP-MMP-3 in transgenic mice leads to mammary hyperplasia and cancer (18, 19). Injection of MMP-11 to MCF-7 cells increases tumor cells (1). However, other studies revealed a decrease in mammary carcinogenesis and tumor cell survival and growth following the very intervention. Expression of MMP-7 in mouse mammary tumor virus (MMTV) (MMTV longterminal receptor promoter enhancer) and MMTV-Her2/neu in transgenic mice promoted premalignant hyperplastic nodules and increased mammary carcinogenesis (20-22). Similar to MMTV-MMP-7, MMTV-MMP-14 expression resulted in mammary hyperplasia and cancer in mice (23), whereas administration of WAP-TIMP-1 and albumin-TIMP-1 in mice reduced mammary neoplasia (24). Possible underlying mechanisms through which MMPs contribute to cancer initiation of breast include: a) releasing some growth factors such as TGF-α (2), b) increasing the bioavailability of growth factors by degrading the binding proteins: for example, cleavage of insulin like growth factor binding proteins (IGF-BPs) by MMPs, consequently releases IGFs or degradation of perlecan by MMPs results in high levels of fibroblast growth factor (FGFs) (25-27), c) regulating growth signals through integrins, d) inducing cell survival and inhibition of cancer cell apoptosis, especially by MMP-11, MMP-9, and partly MMP-7 by means of generating pro-survival proteins such as IGFs, pro heparin-binding EGF-like growth factor (proHB-EGF) and ErbB4 receptor tyrosine kinase. Although MMP-9 and MMP-11 promote cell survival and decrease apoptosis, they induce cell death during development (28-30), e) activation of growth factor receptors; for example, MMP-2 and MMP-9 by degrading ectodomain of FGF receptor1 result in binding of FGF to its receptor (1).

3.5. Role of MMPs in Developing of Breast Cancer and Metastasis

Escape of tumor cells into neighboring tissues, invasion ability, and metastasis to distant sites are contributing factors in aggressiveness of tumors (31, 32). Consequently, facilitation of cancer cell proliferation and growth by misregulation of MMPs contributes to tumor development and metastasis through multiple mechanisms, which are modulated by proteolytic function of MMPs.

Mostimportant ways through which MMPs are involved in tumor invasion include angiogenesis, epithelial-mesenchymal transition, inflammation and immune responses to cancer, and metastasis.

Degradation of ECM facilitates movement of cells. In other words, proteolytic actions of MMPs might lead to uncovering of the crypt sites and presenting novel activity fragment that can modulate tumor development such as migration and angiogenesis (5, 33).

3.6. MMPs Associated With Angiogenesis

Formation of new vessels from existing neighboring blood vessels is a necessary step for tumor progression and growth of a tumor size to approximately 2 mm (1, 2). Angiogenesis consists of 4 main steps: a) remodeling of the surrounding ECM of blood vessels; b) invasion of the surrounding cells by angiogenic signals in endothelial cells; c) migration of endothelial cells as a result of proliferation signals activation, which leads to generating of a column form; d) organization into 3D structure and new capillary (1). MMPs roles in angiogenesis are complex and conflicting. Generally MMPs can promote angiogenesis by two different mechanisms: first, by cleaving ECM and invading endothelial cells; for example, degrading of collagen type 1 is essential for endothelial cell migration and capillary formation (5, 34); and second, stimulation of some growth factors released from ECM sources, which has a major role in promotion or maintenance of the angiogenic phenotypes such as vascular endothelial growth factor (VEGF) and bFGF (34). Some studies have indicated that MMPs, which directly regulate the switch of angiogenesis, including MMP-2, -9, -14 and probably MMP-19, -1 and -13 (34, 35). MMP-2 expression in tumor cells develops angiogenesis by remodeling of collagen type 4 and generating active site to allow for binding of molecules to αvβ3 (36). MMP-9 can regulate and increase bioavailability of pro-angiogenic agents like VEGF (37). MMP-14 acts by cleaving the fibrin matrix that surrounds the vessels, thereby causes more invasion of endothelial cells (38). In the same way, both MMP-1 and MMP-3 can degrade endothelial derived perlecan and stimulate bFGF secretion (34). There is some evidence that indicates MMPs might have inhibitory actions against angiogenesis. Thereby MMP roles are critical, which can negatively regulate the vascular growth (2). For example, MMP-2, -3, -7, -9 and -12 by degrading plasminogen produce angiostatin that potentially inhibits angiogenesis by reducing endothelial cells proliferation. Also MMP-3, -9, -12, and -13 can produce endostatin, which is produced as a breakdown remnant of the basement-membrane collagen type 8 (39-42). Endostatin potentially reduces angiogenesis by means of inhibition of cell proliferation and invasion. Moreover, MMP-12 by degrading the cell membrane bound urokinase-type plasminogen activator receptor can inhibit endothelial cell invasion and angiogenesis (43).

3.7. MMPs and Epithelial-Mesenchymal Transition (EMT)

EMT is a process that occurs during the development of tissues and organs (8). EMT is defined as events such as formation of specific epithelial cells, degradation of the basement membrane, entering of the separated cells, disruption of epithelial tissue constitution, and development of a novel mesenchymal form (44). MMPs have been demonstrated to be important factors in epithelial-mesenchymal transition process in breast cancer progression through 3 mechanisms: a) secretion of MMPs from the surroundings of the tumor leads to induction of EMT in epithelial cells, b) cancer cells express and secrete more MMPs followed by EMT, which in turn increases aggressiveness and metastasis of cells, c) over production of MMPs results in generation of stromal-like cells which induce tumor initiation (4).

3.8. MMPs and Metastasis

Various studies extensively surveyed the MMPs roles in metastasis. Maintaining the stroma integrity and their adhesion together are contributing factors for inhibition of metastasis and invasion of cancerous cells. Due to degrading activity of MMPs during the metastasis in mammary glands, these barriers are disrupted and consequently tumor cells cross the basement membranes and spread to the surrounding stroma. Then, they can invade to blood or lymphatic vessels and be colonized (5). Generally metastasis is modulated by expression of tissue inhibitors of metalloproteinase (TIMPs) and MMPs; over production of TIMPs reduces and MMP-2, -3, -9, -13 and -14 increases metastasis by cleaving collagen type 1 and matrigel (45-51). Only a limited number of cell lines and animal studies have been performed thus far, investigating the role of MMPs in breast cancer metastasis (52). Aggressive manner in MDA-MB-435 human breast cancer cell line was decreased by administration of TIMP-4 into them (53). Also in transgenic models of breast cancer cells, injection of MDA-MB-231 into nude mice by overproduction of TIMP-2 resulted in decreased osteolytic lesions (54). Similar to other steps of breast cancer progression, MMPs promote metastasis through degradation of ECM. Most common MMPs, which modulate invasion of breast cancer, including MMP-2 and MMP-9. These MMPs mediate the invasion by generating collagen 4 of ECM (1). MMP-2 activity leads to disruption of laminin-5, which can trigger cancer cell mobility and migration (55, 56). Moreover, MMP-9 binds to CD44 presented in the cell surface. This localization of MMP-9 is essential for tumor invasion and angiogenesis (5). The most common site, that breast cancer cells invade is bone; this results in disturbing the balance between bone remodeling and formation, and ultimately leading to net bone degradation. Such degradation is the main effect of breast cancer metastasis that is mediated by osteoclasts resorption activity that is catalyzed by MMPs (57).

4. Conclusions

In conclusion, our literature review shows that MMPs are among the factors that play major roles in both activation of all cellular pathways, which lead to breast carcinogenesis, promotion, and metastasis. Administration of MMPs inhibitors in early stage of breast cancer is one of beneficial agents in this regard that can be modulate impaired transduction pathways and prevent tumor cells over proliferation, their invasion, and metastasis. As there are no human studies that support the beneficial effects of MMPs inhibitors, human clinical trial studies are warranted in order to clarify the beneficial effects of MMPs inhibitors application to control the progression and metastasis of the breast cancer. These effects may be considered as an adjuvant therapy in combination with chemotherapy drugs and increase the efficacy of other treatment against breast cancer.

Footnote

Authors' Contributions: Soraiya Ebrahimpour Koujan and Bahram Pourghassem Gargari worked as main study investigator, conception and design of the study and contributed to the manuscript. Mohammad Khalili contributed to the manuscript.

References

1. Duffy MJ, Maguire TM, Hill A, McDermott E, O'Higgins N. Metalloproteinases: role in breast carcinogenesis, invasion and metastasis. *Breast Cancer Res.* 2000;**2**(4):252–7. [PubMed: 11250717]
2. Roy R, Yang J, Moses MA. Matrix metalloproteinases as novel biomarkers and potential therapeutic targets in human cancer. *J Clin Oncol.* 2009;**27**(31):5287–97. doi: 10.1200/JCO.2009.23.5556. [PubMed: 19738110]
3. Lee S, Park HI, Sang QX. Calcium regulates tertiary structure and enzymatic activity of human endometase/matrilysin-2 and its role in promoting human breast cancer cell invasion. *Biochem J.* 2007;**403**(1):31–42. doi: 10.1042/BJ20061390. [PubMed: 17176253]
4. Radisky ES, Radisky DC. Matrix metalloproteinase-induced epithelial-mesenchymal transition in breast cancer. *J Mammary Gland Biol Neoplasia.* 2010;**15**(2):201–12. doi: 10.1007/s10911-010-9177-x. [PubMed: 20440544]
5. Egeblad M, Werb Z. New functions for the matrix metalloproteinases in cancer progression. *Nat Rev Cancer.* 2002;**2**(3):161–74. doi: 10.1038/nrc745. [PubMed: 11990853]
6. Pirouzpanah S, Taleban FA, Atri M, Abadi AR, Mehdipour P. The effect of modifiable potentials on hypermethylation status of retinoic acid receptor-beta2 and estrogen receptor-alpha genes in primary breast cancer. *Cancer Causes Control.* 2010;**21**(12):2101–11. doi: 10.1007/s10552-010-9629-z. [PubMed: 20711807]
7. Sternlicht MD, Werb Z. How matrix metalloproteinases regulate cell behavior. *Annu Rev Cell Dev Biol.* 2001;**17**:463–516. doi: 10.1146/annurev.cellbio.17.1.463. [PubMed: 11687497]
8. Piccard H, Van den Steen PE, Opdenakker G. Hemopexin domains as multifunctional liganding modules in matrix metalloproteinases and other proteins. *J Leukoc Biol.* 2007;**81**(4):870–92. doi: 10.1189/jlb.1006629. [PubMed: 17185359]

9. Yu Q, Stamenkovic I. Cell surface-localized matrix metalloproteinase-9 proteolytically activates TGF-beta and promotes tumor invasion and angiogenesis. *Genes Dev.* 2000;**14**(2):163–76. [PubMed: 10652271]

10. Mori H, Tomari T, Koshikawa N, Kajita M, Itoh Y, Sato H, et al. CD44 directs membrane-type 1 matrix metalloproteinase to lamellipodia by associating with its hemopexin-like domain. *EMBO J.* 2002;**21**(15):3949–59. doi: 10.1093/emboj/cdf411. [PubMed: 12145196]

11. Kajita M, Itoh Y, Chiba T, Mori H, Okada A, Kinoh H, et al. Membrane-type 1 matrix metalloproteinase cleaves CD44 and promotes cell migration. *J Cell Biol.* 2001;**153**(5):893–904. [PubMed: 11381077]

12. McColgan P, Sharma P. Polymorphisms of matrix metalloproteinases 1, 2, 3 and 9 and susceptibility to lung, breast and colorectal cancer in over 30,000 subjects. *Int J Cancer.* 2009;**125**(6):1473–8. doi: 10.1002/ijc.24441. [PubMed: 19507256]

13. Hanahan D, Weinberg RA. The hallmarks of cancer. *Cell.* 2000; **100**(1):57–70. [PubMed: 10647931]

14. Sun Y, Sun Y, Wenger L, Rutter JL, Brinckerhoff CE, Cheung HS. p53 down-regulates human matrix metalloproteinase-1 (Collagenase-1) gene expression. *J Biol Chem.* 1999;**274**(17):11535–40. [PubMed: 10206959]

15. Sun Y, Cheung JM, Martel-Pelletier J, Pelletier JP, Wenger L, Altman RD, et al. Wild type and mutant p53 differentially regulate the gene expression of human collagenase-3 (hMMP-13). *J Biol Chem.* 2000;**275**(15):11327–32. [PubMed: 10753945]

16. Giunciuglio D, Culty M, Fassina G, Masiello L, Melchiori A, Paglialunga G, et al. Invasive phenotype of MCF10A cells overexpressing c-Ha-ras and c-erbB-2 oncogenes. *Int J Cancer.* 1995;**63**(6):815–22. [PubMed: 8847140]

17. Kaya M, Yoshida K, Higashino F, Mitaka T, Ishii S, Fujinaga K. A single ets-related transcription factor, E1AF, confers invasive phenotype on human cancer cells. *Oncogene.* 1996;**12**(2):221–7. [PubMed: 8570199]

18. Sternlicht MD, Lochter A, Sympson CJ, Huey B, Rougier JP, Gray JW, et al. The stromal proteinase MMP3/stromelysin-1 promotes mammary carcinogenesis. *Cell.* 1999;**98**(2):137–46. [PubMed: 10428026]

19. Wiesen JF, Werb Z. The role of stromelysin-1 in stromal-epithelial interactions and cancer. *Enzyme Protein.* 1996;**49**(1-3):174–81. [PubMed: 8797005]

20. Masson R, Lefebvre O, Noel A, Fahime ME, Chenard MP, Wendling C, et al. In vivo evidence that the stromelysin-3 metalloproteinase contributes in a paracrine manner to epithelial cell malignancy. *J Cell Biol.* 1998;**140**(6):1535–41. [PubMed: 9508784]

21. Boulay A, Masson R, Chenard MP, El Fahime M, Cassard L, Bellocq JP, et al. High cancer cell death in syngeneic tumors developed in host mice deficient for the stromelysin-3 matrix metalloproteinase. *Cancer Res.* 2001;**61**(5):2189–93. [PubMed: 11280785]

22. Rudolph-Owen LA, Chan R, Muller WJ, Matrisian LM. The matrix metalloproteinase matrilysin influences early-stage mammary tumorigenesis. *Cancer Res.* 1998;**58**(23):5500–6. [PubMed: 9850086]

23. Ha HY, Moon HB, Nam MS, Lee JW, Ryoo ZY, Lee TH, et al. Overexpression of membrane-type matrix metalloproteinase-1 gene induces mammary gland abnormalities and adenocarcinoma in transgenic mice. *Cancer Res.* 2001;**61**(3):984–90. [PubMed: 11221894]

24. Buck TB, Yoshiji H, Harris SR, Bunce OR, Thorgeirsson UP. The effects of sustained elevated levels of circulating tissue inhibitor of metalloproteinases-1 on the development of breast cancer in mice. *Ann N Y Acad Sci.* 1999;**878**:732–5. [PubMed: 10415821]

25. Manes S, Mira E, Barbacid MM, Cipres A, Fernandez-Resa P, Buesa JM, et al. Identification of insulin-like growth factor-binding protein-1 as a potential physiological substrate for human stromelysin-3. *J Biol Chem.* 1997;**272**(41):25706–12. [PubMed: 9325295]

26. Manes S, Llorente M, Lacalle RA, Gomez-Mouton C, Kremer L, Mira E, et al. The matrix metalloproteinase-9 regulates the insulin-like growth factor-triggered autocrine response in DU-145 carcinoma cells. *J Biol Chem.* 1999;**274**(11):6935–45. [PubMed: 10066747]

27. Whitelock JM, Murdoch AD, Iozzo RV, Underwood PA. The

28. Suzuki M, Raab G, Moses MA, Fernandez CA, Klagsbrun M. Matrix metalloproteinase-3 releases active heparin-binding EGF-like growth factor by cleavage at a specific juxtamembrane site. *J Biol Chem.* 1997;**272**(50):31730–7. [PubMed: 9395517]

29. Schafer B, Marg B, Gschwind A, Ullrich A. Distinct ADAM metalloproteinases regulate G protein-coupled receptor-induced cell proliferation and survival. *J Biol Chem.* 2004;**279**(46):47929–38. doi: 10.1074/jbc.M400129200. [PubMed: 15337756]

30. Sahin U, Weskamp G, Kelly K, Zhou HM, Higashiyama S, Peschon J, et al. Distinct roles for ADAM10 and ADAM17 in ectodomain shedding of six EGFR ligands. *J Cell Biol.* 2004;**164**(5):769–79. doi: 10.1083/jcb.200307137. [PubMed: 14993236]

31. Scorilas A, Karameris A, Arnogiannaki N, Ardavanis A, Bassilopoulos P, Trangas T, et al. Overexpression of matrix-metalloproteinase-9 in human breast cancer: a potential favourable indicator in node-negative patients. *Br J Cancer.* 2001;**84**(11):1488–96. doi: 10.1054/bjoc.2001.1810. [PubMed: 11384099]

32. Remacle AG, Noel A, Duggan C, McDermott E, O'Higgins N, Foidart JM, et al. Assay of matrix metalloproteinases types 1, 2, 3 and 9 in breast cancer. *Br J Cancer.* 1998;**77**(6):926–31. [PubMed: 9528836]

33. Page-McCaw A, Ewald AJ, Werb Z. Matrix metalloproteinases and the regulation of tissue remodelling. *Nat Rev Mol Cell Biol.* 2007;**8**(3):221–33. doi: 10.1038/nrm2125. [PubMed: 17318226]

34. Stetler-Stevenson WG. Matrix metalloproteinases in angiogenesis: a moving target for therapeutic intervention. *J Clin Invest.* 1999;**103**(9):1237–41. doi: 10.1172/JCI6870. [PubMed: 10225966]

35. Kolb C, Mauch S, Peter HH, Krawinkel U, Sedlacek R. The matrix metalloproteinase RASI-1 is expressed in synovial blood vessels of a rheumatoid arthritis patient. *Immunol Lett.* 1997;**57**(1-3):83–8. [PubMed: 9232430]

36. Xu J, Rodriguez D, Petitclerc E, Kim JJ, Hangai M, Moon YS, et al. Proteolytic exposure of a cryptic site within collagen type IV is required for angiogenesis and tumor growth in vivo. *J Cell Biol.* 2001;**154**(5):1069–79. doi: 10.1083/jcb.200103111. [PubMed: 11535623]

37. Bergers G, Brekken R, McMahon G, Vu TH, Itoh T, Tamaki K, et al. Matrix metalloproteinase-9 triggers the angiogenic switch during carcinogenesis. *Nat Cell Biol.* 2000;**2**(10):737–44. doi: 10.1038/35036374. [PubMed: 11025665]

38. Hiraoka N, Allen E, Apel IJ, Gyetko MR, Weiss SJ. Matrix metalloproteinases regulate neovascularization by acting as pericellular fibrinolysins. *Cell.* 1998;**95**(3):365–77. [PubMed: 9814707]

39. Dong Z, Kumar R, Yang X, Fidler IJ. Macrophage-derived metalloelastase is responsible for the generation of angiostatin in Lewis lung carcinoma. *Cell.* 1997;**88**(6):801–10. [PubMed: 9118223]

40. Cornelius LA, Nehring LC, Harding E, Bolanowski M, Welgus HG, Kobayashi DK, et al. Matrix metalloproteinases generate angiostatin: effects on neovascularization. *J Immunol.* 1998;**161**(12):6845–52. [PubMed: 9862716]

41. Gorrin-Rivas MJ, Arii S, Furutani M, Mizumoto M, Mori A, Hanaki K, et al. Mouse macrophage metalloelastase gene transfer into a murine melanoma suppresses primary tumor growth by halting angiogenesis. *Clin Cancer Res.* 2000;**6**(5):1647–54. [PubMed: 10815882]

42. Ferreras M, Felbor U, Lenhard T, Olsen BR, Delaissé JM. Generation and degradation of human endostatin proteins by various proteinases. *FEBS Lett.* 2000;**486**(3):247–51. doi: 10.1016/s0014-5793(00)02249-3.

43. Koolwijk P, Sidenius N, Peters E, Sier CF, Hanemaaijer R, Blasi F, et al. Proteolysis of the urokinase-type plasminogen activator receptor by metalloproteinase-12: implication for angiogenesis in fibrin matrices. *Blood.* 2001;**97**(10):3123–31. [PubMed: 11342439]

44. Shook D, Keller R. Mechanisms, mechanics and function of epithelial-mesenchymal transitions in early development. *Mech Dev.* 2003;**120**(11):1351–83. [PubMed: 14623443]

45. Ahonen M, Baker AH, Kahari VM. Adenovirus-mediated gene delivery of tissue inhibitor of metalloproteinases-3 inhibits invasion and induces apoptosis in melanoma cells. *Cancer Res.*

degradation of human endothelial cell-derived perlecan and release of bound basic fibroblast growth factor by stromelysin, collagenase, plasmin, and heparanases. *J Biol Chem.* 1996; **271**(17):10079–86. [PubMed: 8626565]

1998;**58**(11):2310–5. [PubMed: 9622064]

46. Lochter A, Galosy S, Muschler J, Freedman N, Werb Z, Bissell MJ. Matrix metalloproteinase stromelysin-1 triggers a cascade of molecular alterations that leads to stable epithelial-to-mesenchymal conversion and a premalignant phenotype in mammary epithelial cells. *J Cell Biol*. 1997;**139**(7):1861–72. [PubMed: 9412478]

47. Belien AT, Paganetti PA, Schwab ME. Membrane-type 1 matrix metalloprotease (MT1-MMP) enables invasive migration of glioma cells in central nervous system white matter. *J Cell Biol*. 1999;**144**(2):373–84. [PubMed: 9922462]

48. Deryugina EI, Luo GX, Reisfeld RA, Bourdon MA, Strongin A. Tumor cell invasion through matrigel is regulated by activated matrix metalloproteinase-2. *Anticancer Res*. 1997;**17**(5A):3201–10. [PubMed: 9413149]

49. Ala-Aho R, Johansson N, Baker AH, Kahari VM. Expression of collagenase-3 (MMP-13) enhances invasion of human fibrosarcoma HT-1080 cells. *Int J Cancer*. 2002;**97**(3):283–9. [PubMed: 11774278]

50. Itoh T, Tanioka M, Matsuda H, Nishimoto H, Yoshioka T, Suzuki R, et al. Experimental metastasis is suppressed in MMP-9-deficient mice. *Clin Exp Metastasis*. 1999;**17**(2):177–81. [PubMed: 10411111]

51. Itoh T, Tanioka M, Yoshida H, Yoshioka T, Nishimoto H, Itohara S. Reduced angiogenesis and tumor progression in gelatinase A-deficient mice. *Cancer Res*. 1998;**58**(5):1048–51. [PubMed: 9500469]

52. Davies B, Miles DW, Happerfield LC, Naylor MS, Bobrow LG, Rubens RD, et al. Activity of type IV collagenases in benign and malignant breast disease. *Br J Cancer*. 1993;**67**(5):1126–31. [PubMed: 8494711]

53. Wang M, Liu YE, Greene J, Sheng S, Fuchs A, Rosen EM, et al. Inhibition of tumor growth and metastasis of human breast cancer cells transfected with tissue inhibitor of metalloproteinase 4. *Oncogene*. 1997;**14**(23):2767–74. doi: 10.1038/sj.onc.1201245. [PubMed: 9190892]

54. Yoneda T, Sasaki A, Dunstan C, Williams PJ, Bauss F, De Clerck YA, et al. Inhibition of osteolytic bone metastasis of breast cancer by combined treatment with the bisphosphonate ibandronate and tissue inhibitor of the matrix metalloproteinase-2. *J Clin Invest*. 1997;**99**(10):2509–17. doi: 10.1172/JCI119435. [PubMed: 9153295]

55. Oh J, Takahashi R, Kondo S, Mizoguchi A, Adachi E, Sasahara RM, et al. The membrane-anchored MMP inhibitor RECK is a key regulator of extracellular matrix integrity and angiogenesis. *Cell*. 2001;**107**(6):789–800. [PubMed: 11747814]

56. Koshikawa N, Giannelli G, Cirulli V, Miyazaki K, Quaranta V. Role of cell surface metalloprotease MT1-MMP in epithelial cell migration over laminin-5. *J Cell Biol*. 2000;**148**(3):615–24. [PubMed: 10662785]

57. Lochter A, Bissell MJ. An odyssey from breast to bone: multi-step control of mammary metastases and osteolysis by matrix metalloproteinases. *APMIS*. 1999;**107**(1):128–36. [PubMed: 10190289]