

Role of Matrix Metalloproteinases in Animals

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Abstract

Matrix metalloproteinases are a family of calcium-dependent and zinc-dependent endopeptidases, which excrete from many cell types. These enzymes can hydrolyze extracellular matrix proteins. The most important inhibitor of MMPs is tissue inhibitors of metalloproteinases (TIMPs). The imbalance between MMPs and TIMPs causes pathological condition in human and animals. This review focuses on structural, role and several reports of MMPs in horse, dog, cat, fish and avian. Over production of MMPs is associated with tissue destruction and erosion of cartilage in equine osteoarthritis, especially MMP-2 and MMP-9. In canine and feline, many evidences reported about MMPs and cancer such as MMP-2 and MMP-9. MMPs can promote cancer progression by increasing cancer cell migration, invasion and metastasis. .

Keywords: cancer, canine, equine, feline, matrix metalloproteinase, osteoarthritis

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บทคัดย่อ

บทบาทของเอนไซม์ Matrix metalloproteinases ในสัตว์

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เอนไซม์ matrix metalloproteinases (MMPs) เป็นเอนไซม์ที่จัดอยู่ในกลุ่ม endopeptidase ที่ต้องการแคลเซียมและสังกะสี เอนไซม์นี้หลั่งออกมาจากเซลล์หลายชนิด และทำหน้าที่ย่อยโปรตีนที่เป็นส่วนสำคัญสำหรับ extracellular matrix ตัวยับยั้งเอนไซม์นี้ที่สำคัญคือ tissue inhibitor of metalloproteinases (TIMPs) การจับกันแบบไม่สมดุลระหว่าง MMPs และ TIMPs ทำให้เกิดพยาธิสภาพหลายแบบในคนและสัตว์เลี้ยง ซึ่งบทความนี้เน้นในเรื่องของโครงสร้างและหน้าที่ของ MMPs รวมถึงรายงานบทบาทของ MMPs ใน ม้า สุนัข แมว ปลา และ สัตว์ปีก ในน้ำนั้น MMPs ที่มีปริมาณมากจะทำให้กระดูกอ่อนบริเวณข้อต่อเสียหาย และทำให้เกิดภาวะข้ออักเสบตามมา โดยเฉพาะ MMP-2 และ MMP-9 ในสุนัขและแมวนั้นมีการศึกษาบทบาทของ MMPs เช่น MMP-2 และ MMP-9 กับโรคกระดูกหลายชนิดพบว่า MMPs มีบทบาทต่อการเคลื่อนที่ของเซลล์มะเร็ง และการแพร่กระจายไปยังส่วนอื่นๆของร่างกาย

คำสำคัญ: มะเร็ง สุนัข ม้า แมว matrix metalloproteinase ข้ออักเสบ

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Introduction

Matrix metalloproteinases (MMPs) were discovered in 1962, first detected as metamorphogenic activity in tadpole tails (Gross and Lapiere, 1962). MMPs are a large family of extracellular matrix (ECM) - degrading enzymes that shares common functional domains and activation mechanisms. These are calcium- and zinc-dependent endopeptidase. All MMPs are secreted as a zymogen or a pro-MMP which is an inactive or latent form. These latent MMPs need to be activated in order to be able to cleave ECM components (Maskos and Bode, 2003). MMPs play an important role in functions of the ovarian, remodeling of tissue during embryo development, cell migration, wound healing, and tooth development. They are regulated by hormones, cytokines and growth factors, and excreted by a number of connective tissue and pro-inflammatory cells including osteoblasts, fibroblasts, endothelial cells, neutrophils and lymphocytes. MMPs are inhibited by several type of inhibitors, tissue inhibitors of metalloproteinases (TIMPs) are the most important (Brew et al., 2000). The balance between MMPs and TIMPs is responsible for control of ECM degradation (Bode et al., 1999). Disruption of MMP-TIMP balance can result in pathologies such as osteoarthritis, atherosclerosis, vascular disease, heart failure, pulmonary emphysema, central nervous system disease, cirrhosis, tumor growth, tumor cell invasion and metastasis (Kottinen et al., 1999; Tetlow et al., 2001; Baker et al., 2002).

Type and Structure of Matrix metalloproteinase

Matrix metalloproteinases are classified into 28 members and 10 subgroups based on their structure. Subgroup of MMPs are collagenases (MMP-1, MMP-8, MMP-13, MMP-18), gelatinases (MMP-2, MMP-9), stromelysins (MMP-3, MMP-10, MMP-11), matrilysins (MMP-7, MMP-26), furin-activated secreted MMP (MMP-11, MMP-28), transmembrane type (MMP-14, MMP-15, MMP-16), GPI-linked membrane type (MMP-17, MMP-24, MMP-25), vitronectin-like insert MMP (MMP-21), Cys/Pro-Rich IL-1 receptor like domain MMP (MMP-23) and no group designation (MMP-12, MMP-19, MMP-20, MMP-27, MMP-28) (Yong et al., 2001; Krizkova et al., 2011). Molecular weights of MMPs (latent form) range from 28,000 to 76,000 Da. The smallest MMP is MMP-7, which has molecular weight (latent/active) of 28,000/19,000 Da. The biggest MMP is MMP-9, which has molecular weight (latent/active) of 76,000/67,000 Da.

Most of the matrix metalloproteinase consist of four domains, which are single peptide (SP), pro-peptide domain, catalytic and zinc binding domain and C-terminal hemopexin domain (Liacini et al., 2002). The membrane type MMPs (MT-MMPs) contain an extra transmembrane domain. All MMPs are synthesized in the cell and secreted to the extracellular space. Their mRNA specifies a hydrophobic signal sequence typically comprising 18-30 residues, termed single peptide. This region is cut off during transit from the cell and is not observed in mature enzymes recovered from outside the cell. The propeptide domain extends from the N- terminal created after removal of the single peptide to the

beginning of the catalytic domain, a length typically spanning 80 amino acids. This propeptide domain keeps enzyme in an active form since the cysteine residue 73 in a conserved sequence, PRCG(V/N)PD, is positioned directly opposite the zinc atom at the active center and is coordinated to it through the -SH group. This is termed cysteine switch because displacement of cysteine residues by a wide variety of means (oxidation, proteolytic cleavage, etc.) would turn on the enzyme activity. Catalytic and zinc domain is the segment that contain catalytic zinc. The C-terminal portion of the catalytic zinc binds in the sequence HELGHXXGXXH by the three His residues. This domain is responsible for substrate hydrolysis and control of the characteristic specificity for substrates of MMPs. The C-terminal hemopexin domain has a four-bladed propeller structure in the middle containing calcium ion. This domain contributes to substrate specificity and could be bound to components of the extracellular matrix and heparin.

Collagenases and Stromelysins contain single peptide (SP), propeptide domain, catalytic and zinc binding domain and C-terminal hemopexin domain (Fig 1). Matrilysins lack C-terminal hemopexin domain and hinge region. Furin-activated secreted MMPs have a furin recognition motif in their catalytic domain for intracellular activation. These MMPs are activated by furin in the *trans*-Golgi network and are secreted in their active form. Transmembrane MT-MMPs have transmembrane binding domain and GPI-linked MT-MMPs contain GPI domain in the C-terminal. In the gelatinases, fibronectin (FN)-like type II repeats are also present in the catalytic domain. Cys/Pro-Rich IL-1 Receptor like domain MMP has an NH₂-terminal signal anchor and a cysteine-rich, proline-rich, interleukin-1-like domain instead of C-terminal hemopexin domain (Krizkova et al., 2011; Yong et al., 2001; Egeblad and Werb, 2002).



Figure 1 Structure of Matrix metalloproteinase (subgroup Collagenases)

Role of Matrix metalloproteinase

MMP activity is regulated by TIMPs, which are known to inhibit all MMPs. TIMPs can inhibit MMPs by the formation of a 1:1 complex (Visse and Nagase, 2003). The remodeling of normal and abnormal tissue is regulated by MMPs and TIMPs balance. The remodeling of tissue is essential for physiology, including embryo development, collagen turn over, tooth development, cell migration and wound healing (Patricia et al., 2005). Imbalance between MMPs and TIMPs causes pathological conditions such as osteoarthritis, rheumatoid, atherosclerosis, vascular disease, heart failure, pulmonary emphysema, central nervous system disease, cirrhosis, tumor growth, tumor cell invasion and metastasis in human being and in some animals (Patricia et al., 2005; Kizkova et al., 2011). MMPs are

involved in wound healing which involves the migration of keratinocytes at the edge of the wound to re-epithelialize the damaged surface. MMPs are found in pulpal tissue and odontoblasts and play role in dentin matrix formation (Biljana et al., 2011). In cancer, role of MMPs can be mainly attributed to many steps in carcinogenic process such as tumor growth, angiogenesis, tumor cell invasion and metastasis (Klein et al., 2004). MMPs conduct microenvironment for primary tumor growth by releasing ECM-bound growth factors and then bind with extracellular matrix proteins which control cell proliferation, differentiation and synthesis and remodeling of extracellular matrix. MMPs also degrade ECM in the beginning steps of tumor angiogenesis and these enable endothelial cells to migrate followed by proliferation, finally resulting in new vessel formation (Rundhaug, 2003). Tumor cell secretes many kinds of protease including MMPs to breakdown blood vessel basement membrane and migrate or invade into the surrounding stroma. Then, tumor cells enter into the circulation (intravasation), exit from the circulation (extravasation) and grow in the metastatic site (Rundhaug, 2003). MMPs are also secreted by both synovial cells and chondrocytes. Overproduction of MMPs is related with tissue destruction in the lamellar basement membrane and erosion of articular cartilage in osteoarthritis (Konttinen et al., 1999; Tetlow et al., 2001).

Matrix metalloproteinase in equine

In horse, several evidences of MMPs activity related with osteoarthritis and the type of MMPs which correlated with osteoarthritis are MMP-1, MMP-2, MMP-9, and MMP-14. MMP-2 and MMP-9 are elevated in equine joint diseases. An active form of MMP-2 and MMP-9 is elevated as an additional diagnostic tool in diagnosis osteoarthritis (Zrimsek et al., 2007). Report in 2004 showed that MMP-1 activity was also increased in synovial fluid of osteoarthritis and the elevation of MMP-1 probably reflected pathological matrix degradation. (Brama et al., 2004; Fietz et al., 2008). MMP-1 activity level is high in synovial fluid of fetal joint and after birth this level declines gradually. In osteoarthritis horses, the level of MMP-1 activity increases but exercise does not influence MMP-1 activity (Brama, 2000). Nevertheless, the report in 2009 suggested that MMP-1 and IL-8 genes were both involved in the exercise-induced stress response. Transcription of MMP-1 and IL-8 is found to be up-regulated in horse with endurance exercise and down-regulated in 24 hours (Cappelli et al., 2009). MMP-14 located in the cytoplasm of lamellar basal cells disappears during laminitis development. These enzymes play a role in laminitis and inhibition of their activity to prevent laminitis (Kyaw-Tanner et al., 2008). In horse, MMPs are quite important in osteoarthritis and the measurement MMPs activity in synovial fluid might be a key marker for early diagnosis of equine osteoarthritis.

Matrix metalloproteinase in canine and feline

In canine, many reports showed the variety pathological condition such as arthritis, cardiomyopathy, keratoconjunctivitis and cancer. In

canine rheumatoid arthritis resulted in increase of MMP-2 and MMP-9 levels in synovial fluid and then MMPs could degrade several extracellular matrix molecules including collagen types IV, V and X, elastin and proteoglycan core protein in the articular cartilage (Coughlan et al., 1998). Increased pro-MMP-9 levels occur in the myocardium in canine dilated cardiomyopathy. Proteolytic enzyme including MMPs is implicated in the degradation and remodeling of collagen which is major component of the myocardium (Gilbert et al., 1997). Gelatinase activity was increased in fluids from eyes of dog with keratoconjunctivitis (Arıcan et al., 1999). There are many reports about MMPs in many kinds of canine tumors such as MMP-2 and MMP-9. MMP-2 and MMP-9 were detected in canine osteosarcoma and MMPs activity in tumor was higher than unaffected stromal tissue, indicating that MMPs might be involved in tumor growth and metastasis. MMPs could degrade extracellular matrix and basement membrane of surrounding tissue and blood vessels via metastasis. (Lana et al., 2000). MMP-2 and MMP-9 were also detected in canine mast cell tumor and mammary gland tumor in protein level (Leibman et al., 2000; Shia et al., 2011). MMP-9 is highly expressed in canine mammary adenocarcinoma tissues and MMP-9 activity is high in serum. In serum, measurement of MMP-9 level by zymography assay is correlated with tumor grade benign and malignant. MMP-9 is an important enzyme to degrade basement membrane which is a first barrier for tumor cells in metastasis. Therefore, the level of serum MMP-9 activity might be a marker for early diagnosis of adenocarcinoma (Yokota et al., 2001). In malignant melanomas, MMP-9 was overexpressed and no significant difference in MMP-2 and MT1-MMP was found (Docampo et al., 2011). The report in 2003 found that tumor produced significantly higher MMP-2 and MMP-9 than non-tumors, malignancies significantly higher total MMPs levels than benign tumors, and sarcomas had higher MMP-2 than carcinoma (Loukoulos et al., 2003). In canine oronasal tumor, melanoma and squamous cell carcinoma also found increased level of MMP-2 activity and MMP-2/TIMP-2 ratio might be a value in evaluating the prognosis in canine oronasal cavity tumors (Nakaichi et al., 2007). In canine chondrosarcomas, there were significant increase in expression of collagenases (MMP-1 and MMP-13), suggesting that enzyme collagenases might play an important role in the progression of chondrosarcoma (Kuroki et al., 2002). However, there are fewer reports about MMPs in cat and mostly are about sarcoma. Serum MMPs concentration is increased in cat with sarcoma and carcinoma by zymography assay. However, poor correlation was found between serum and tissue MMP levels of increasing histological grades of sarcoma and carcinoma (Jankowski, 2002). A report in 2009 found that MMP-2 values of feline meningiomas were significantly higher than those of canine whereas the tendency of MMP-9 levels was decreased during a follow-up from the 23rd month to the 44th month by immunohistochemical and image analysis quantification method (Mandara et al., 2009). In dogs,

MMP activity is detected in higher level in malignant tumors than benign tumors and non-tumors. Therefore, MMPs might be suggested as a useful marker for early diagnostic of cancer patient and could be a tool for prognosis of cancer treatment.

Matrix metalloproteinase in fish

Role of MMPs in fish was reported in field of embryo development, reproduction and immune response. In zebra fish, MMP-13 was expressed highest at 48 hour after fertilization. It means that MMP-13 is necessary for normal zebra fish embryogenesis (Hillegass et al., 2007). MT5-MMP (MMP-24) is found in fish oocytes, suggesting their involvement in the process of spawning. In Medaka fish, it plays a role in ovulated oocytes and fertilized eggs (Kimura et al., 2001). In carp, MMP-9 serves a function in immune responses since it was expressed in peritoneal and peripheral blood leukocytes (Chadzinska et al., 2008). Gallbladder from 2 fish species, mullet (*Mugil liza*) and tilapias (*Tilapia rendalli*) contains substantial MMPs. They suggested that MMPs in fish bile may be involved in detoxification processes and contaminant protection (Hauser-Davis et al., 2012).

Matrix metalloproteinase in avian

In avian, MMPs play a role in growth-plate vascularization and ossification. They participate in proteolytic cleavage and remodeling of ECM. Tibial dyschondroplasia (TD) is a skeletal abnormality in avian species which is characterized by the formation of a nonvascularized and nonmineralized plaque in the growth plate. MMPs (MMP-2, MMP-3, MMP-9 and MMP-13) decrease in TD lesion and reappear during recovery of growth plate. MMPs play role in recovery process of TD (Dan et al., 2009). Mechanism of MMP regulation in growth plate is different between chicken and turkey (Simsa et al., 2007). MMP-3, MMP-9, and MMP-13 plays a role in the vascularization and ossification processes, whereas MMP-2 is related to chondrocyte differentiation and may be involved in cartilage remodeling in the avian growth plate (Hasky-Negev et al., 2008). However, MMP-9 correlates with cartilage collagen loss in chick embryo tibias cultured with lipopolysaccharide and this enzyme contains glycosaminoglycan chains (Patchigolla et al., 2012). According to a report in 2001, the bile from turkey (*Meleagris gallopavo*) gall bladder was found to contain substantial MMP activities but the physiological roles of bile MMPs was not clear (Rath et al., 2001).

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