j.Egypt.net.med.Assoc 79, no 3. 761 – 771 (2019)

UPDATED REVIEW ON MATRIX METALLOPROTEINASES:ROLE, CLASSIFICATION AND ITS INHIBITORS

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ABSTRACT

Matrix Metalloproteinases "MMPs" are zinc -dependent enzymes , that destruct many types of proteins of the extracellular matrix (ECM).MMP families includes collagenases, gelatinases, stromelysin, matrilysins and membrane-type MMPs.

MMPs regulate many biological processes such as healing, repair, vascular remodeling and angiogenesis. Matrixins are calcium-dependent zinc containing endopeptidases. Other family members such as adamalysins, seralysins and astacins also recorded. Membrane - type matrix metalloproteinases (MT-MMPs) constitutes subgroup of the matrix metalloproteinase (MMP), and there are 6 MT-MMPs in humans. MT-MMPs are further sub-classified into type 1 transmembrane - type (MT1, MT2, MT3, and MT5-MMPs) and glucosylphosphodylinositol (GP1) - anchored type (MT4- and MT6-MMPs). Matrix Metalloproteinases (MMPs) degrade all components of the matrix (CM) and numerous non-matrix proteins. Increased MMP-2 activity is also involved in the proteolysis of important intra cellular targets in cardiomyocytes and vascular smooth muscle cells (VSMC**).**Matrix metalloproteinases (MMPs) played a principle role in many of the cell functions and keeping its homeostasis. Also, shared in different pathological abnormalities such as inflammation and hurried many disease progression. MMP-9 at the same time is widely related to carcinogenesis and considered as biomarker to various types of cancers as detected by recent researches. The aim of the present review is to throw a light on the role of matrix metalloproteinases (MMPs) in both physiological and pathological processes. The study will increase the information about the diseases associated with MPPs as well as the updated classifications and its inhibitors that helped in treatment as well as protect against many pathological conditions.

Keywords:

Matrix metalloproteinases, Classification, Physiology, Pathology, Inhibitors.

INTRODUCTION

Matrix metalloproteinases (MMPs) damage the constituents of the extra cellular matrix (ECM). MMPs consists of nine or more highly similar Zn (+2) endopeptidases **(Birkedal *et al.,* 1995)**. MMPs expression is controlled at all transcription levels, except MMP-8 and MMP-9 arrangement in neutrophils. The role of many external factors impacting transcriptional activation detected. These factors include ECM molecules , such as inflammatory cytokines , hormones and growth factors .Growth factors such as transforming growth factor beta (TGF Beta) , epidermal growth factor receptor (EGFR) , tumor necrosis factor - alpha (TNF-alpha) and Interleukin -1 beta (IL-1 Bata). Matrix metalloproteinases (MMPs) are enzymes that cleave chemokines, and shed cell membrane proteins during homeostatic process in the cells **(Alfranca *et al.,* 2008 and Yen *et al.,* 2011 and Bonnans *et al.,* 2014)**.

Matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) are considered to be key mediators of tumor invasion and metastasis in dogs. MMP-2 was significantly more expressed in papillary meningioma in dogs. **(Mandara *et al*., 2017).**

Matrix metalloproteinases (MMPs) played an important role in remodeling of the ECM in both normal homeostasis and pathological states. The recent data cleared that a relationship between MMP expression and activity in vivo at various levels, from gene expression to zymogen activation and endogenous inhibition. **(Gaffinely*et al.,*2015)**.

Matrix metalloproteinases (MMPs) shared in the development , metamorphosis, remodeling , cell regeneration and induction of diseases as well as other roles of MMPs besides the MMPs inhibitors were also studied **(Sunday and Newry, 2015) .** Collagenolysis is essential in cell development, homeostasis and contributes in many other responses. Interstitial collagenolytic enzymes in mammals as a members of metalloproteinase (MMP) and Cathepsin K. The use of knockout and mutant Rat models is reflect on human diseases and closely regulated to the collagenolytic roles of MT1-MMP"Membrane type-1 matrix metalloproteins" and MMP-13 **(Amar *et al* .,2017).** Matrix metalloproteinases (MMPs) did a principle role in many cell functions. Also, caused different pathological abnormalities such as inflammation and induction of much disease **(Beutel *et al.,* 2018).** MMP-2 activity is also involved in the proteolysis of cardiomyocytes and vascular smooth muscle cells (VSMC**) (Beutel *et al.,* 2018).**The matrix metalloproteinase (MMP) is a group of enzymes ,that modulates the tissue

structural components and this a process is required for tissue repair , proliferation , apoptosis and angiogenesis .Miss expression of MMPs in endometrial cells and the surrounding tissues is a critical factor in promoting the attachment , invasion and angiogenesis that required for establishment of endometriosis **(Alali *et al.*,2018).** MMP-9 is an important metalloproteinases, which plays a vital role in different biological processes. MMP-9 separate many ECM proteins, that helping in regulation the ECM remodeling. It can also cleave many plasma surface proteins to release them from the surface .MMP-9 at the same time is widely related to carcinogenesis and considered as biomarker to various types of cancers as detected by recent researches **(Hao, 2018)** MMP-9 regulates both inflammatory and injury processes It degrades various types of proteins and shared in many other pathological conditions such as swine flu and Influenza virus infection .In case of H1N1 the level of MMP-9 is increased in the alveolar epithelial cells and leukocytes .MMP-9 deficiency in lung cells had complete protection for mice against H1N1 infection. Authors believed that MMP-9 is a novel therapeutic target for IAV infection. **(Rojas *et al.*, 2018)**.

The role of MMPs in Physiological compared to Pathological Processes:

Table (1): showed the role of MMPs in many physiological and pathological processes.

physiological processes	Pathological processes
Endometrial cycling and ovarian follicles rupture (Estrus cycle)	Rheumatoid Arthritis and Osteoarthritis
Bone Remodeling and embryonic development (ECM-remodeling/MMP-9). Correlated to the arrangement of the ECM ,cell hypertrophy and migration	Cancer growth, invasion and metastasis Cancer Biomarker (MMP-9). Endothelial cells proliferation.
Wound repair and healing	Gastric ulcer and Corneal ulceration
Apoptosis	Liver cirrhosis and Fibrotic lung disease
Nerve regeneration and growth	Pathological Apoptosis
Macrophage function	Otosclerosis
Neutrophil function.	Atherosclerosis
Skeletal bone growth.	Multiple sclerosis
Enamel maturation	Aortic aneurysm
Primary tooth resorption	Epidermolysis bullosa
Regulate the activity of cell membrane receptors as well as post-receptor signaling mechanisms	Hypertension, and Aneurysm
Regulates both inflammatory and injury processes	Idiopathic Pulmonary Fibrosis
cell functions and keeping its homeostasis	H1N1 and Influenza A virus infections(MMP-9)
Tissue morphogenesis	Kawasaki disease
Collagenolysis, cell development and homeostasis. (MTI-MMP/MMP-13.	Inflammation and Disease progression
Lysis of cell surface proteins (MT1-MMP)	HIV, MS, OP, RA, Stroke, Alzheimer's disease, Cancer and Hepatitis C virus.
Cleave the all constituents of ECM	MMP-1, MMP-2, MMP-3 and MMP-9 (HIV infection.
Angiogenesis	Multiple carcinomas and acute myeloid leukemia (MMP-7&MMP-15).
Activate many cellular behaviors	Human Reproductive Disorders
Embryonic development	Endometeriosis
	MMP-2--Control breast cancer metastasis to the bone (2018)
	Progression of osteosarcoma (OS) via increasing the activity of tumor growths, invasion as well as tumor metastasis (MMP-9).
	MMP-2 in cardiomyocytes and VSMC, degrad ed and contribute in contractile dysfunction, cell hypertrophy or migration (hypertension.)
	GBM+ Traumatic brain injury, MS and Stroke (MMPs).

The Physiological role of matrix metalloproteinases:

A study examined how pericellular collagen membrane-type 1 matrix metalloproteinase (MT1-MMP) interacts with the process of binding the substrates**.** MMP regulate the activity of cell membrane receptors as well as post-receptor signaling mechanisms and so affects the cell function. Assessment the pivotal role of MMPs was done by measuring their mRNA expression protein levels and proteolytic activity using Gel Zymography. Also, MMPs activity regulated by MMP/TIMP balance, could determine the net of MMPs activity.

The use of knockout and mutant animal models is reflect on human diseases and closely regulated to collagenolytic roles of matrix inhibitors-1 and MMP-13. Authors studied the effects of oral administration of bifid bacterium animals subsp.lactis BB-12 and Lactobacillus rhamnosus GG on the salivary levels of Matrix metalloproteinases (MMP-8 and MMp-9) and the tissue inhibitors (TIMP-1) in healthy adults. **(Verma and Hansch, 2007and Itoh, 2015**, **found)** that MMp - 9 level was increased in probiotic group and the level of TIMP-1 was decreased indicating that probiotics have immunomodulatory effects in the oral cavity. Furthermore , increased salivary MMP-9 levels may be an indication of the defense potential matrix proteinases **(Cerofolin *et al* ., 2016 ; Liu and Khalil , 2017 ; Amar *et al* ., 2017 and Jasberg *et al* ., 2018)**.

The pathological roles of matrix metalloproteinases:

Matrix metalloproteinases (MMPs) are Broadband network in several diseases such as HIV, MS, OP, RA, Stroke, Alzheimer's disease, Cancer and Hepatitis C virus. The increased activity of MMPs leads to ECM breakdown that shared in many pathological alterations such as Kawasaki disease besides severe endothelial cells damage. MMPs and its tissue inhibitors (TIMP) gene considered as a predisposing players in human reproductive disorders. MMPs such as MMP-2, MMP-9 and its inhibitors (MT1-MMP) are involved in many types of canine mammary gland tumor progression **(Luca *et al*., 2011).** A regulation disturbance of metalloproteinases (MMPs) is considered one of the main toxic backgrounds of sulfur mustard(SM).Leuckocyticcells accumulation,decreased tissue inhibitors of metalloproteinases (TIMPs), increased pro-inflammatory mediators ,as well as a massive production of ROS are the possible mechanisms by which ,the SM induced their expression for long time. Matrix metalloproteinases (MMPs) are proteolytic enzymes which their roles presented in many pathological conditions such as cancer production and metastasis.

The role of MMP-2 in controlling breast cancer metastasis to the bone studied by some investigators. Matrix metalloproteinase-9 (MMP-9) had a significant role in progression of osteosarcoma (OS) via increasing the activity of tumor growths, invasion as well as tumor metastasis.

The pathophysiological role of MMPs in endometriosis:

Was studied .Miss expression of MMPs in endometrial cells or the surrounding tissues are critical factors in promoting the attachment, invasion as well as angiogenesis that required for establishment of endometriosis. Hypertension resulted from maladaptive responses of both vascular and cardiac remodeling, which are correlated to the arrangement of the ECM, cell hypertrophy and migration as well as MMPs defectives and showed in many pathological conditions such as hypertension, atherosclerosis and aneurysm. Increased MMP-2 activity also involved in the proteolysis of important intracellular targets in cardiomyocytes and vascular smooth muscle cells (VSMC).Troponin I and Calponin-1 are some of the targets of MMP-2 in cardiomyocytes and VSMC respectively that contributes in the contractile of the myocardial cells, dysfunction and cardiac cell hypertrophy. MMP - 2 may be activated by S-glutathiolation in vitro by peroxynitrite , which free the pro-peptide domain from the catalytic site and generates the activity of 72KDa MMP-2. Glioblastoma multiforme (GBM) is one of the most destructive cancers, with modest advances in overall survival despite significant improvements in imaging, surgery and molecular genomic understanding.

MMPs are major players in GBM invasion and considered a pathological hallmark of tumors. MMP-9 is widely related to carcinogenesis and considered as biomarker to various types of cancers as detected by recent researches. MMP-9 regulates both inflammatory and injury processes. It degrades various types of proteins and shared in many pathological conditions such as H1N1 and IAV infection. In case of H1N1 the level of MMP-9 is increased in the alveolar epithelial cells and leukocytes. MMP-9 deficiency in lung cells had complete protection for mice against H1N1 infection. Several members of MMPs, including MMP-1, MMP-2, MMP-3 and MMP-9, representing a huge role in HIV progression, which showed severe neurological disturbance during examination of the affected patients**.** MMP-7 and MMP-15 are highly expressed in multiple carcinomas and acute myeloid leukemia. Membrane-type 1 matrix metalloproteinase were studied by paramagnetic nuclear magnetic resonance relaxation enhancement (PREs), fluorescence and mutagenesis. **(Hideaki *et al* .,**

2001;Alali *et al.*, 2018 ;Ali *et al* .,2018; Barisic *et al* ., 2018 ;Hao ,2018 ; Marilena and Conor , 2018; Parente and Castro,2018;Pullen *et al*.,2018;Rojas *et al*.,2018;Zhou *et al* .,2018 ; Marcink *et al* ., 2019 ;Singh *et al* ., 2019 and Wu *et al* ., 2019).

Classifications of MMPs:

The MMPs are classified into.

Evolutionary:

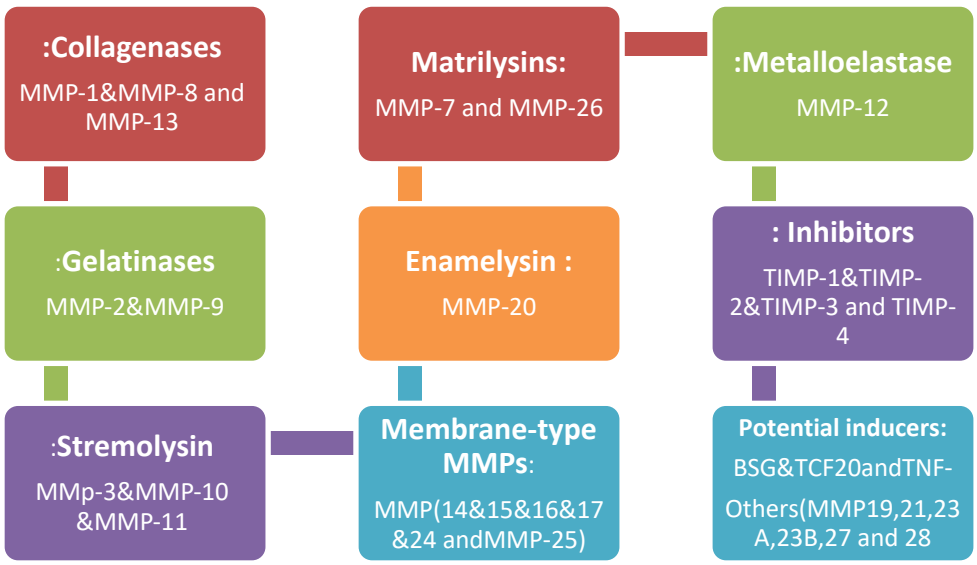
By the use of bioinformatics method to compare the primary sequencing of the MMPs as mentioned in Fig. (1).

Functional:

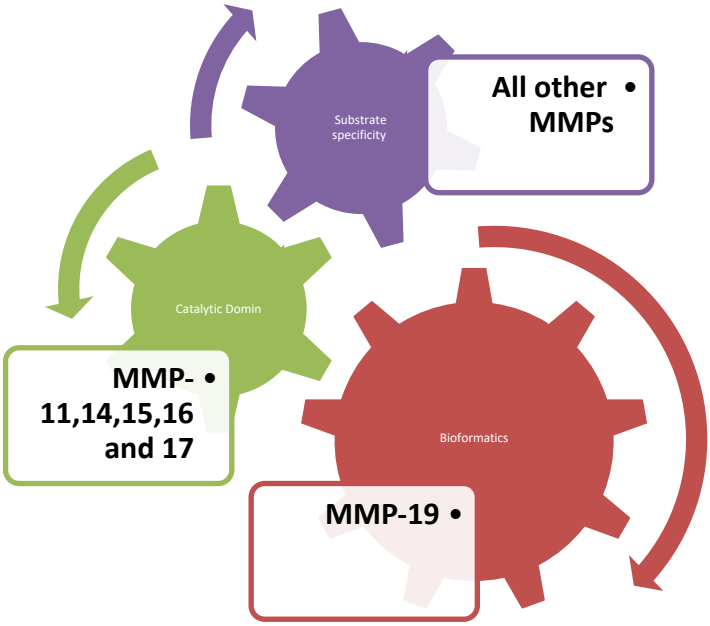
Most common used groupings are based on historical evaluation of the MMPs and the cellular localization of the MMP. The identified groups are collagenases, the gelatinases the stromalysins, Matrilysins, Enamelysin, metalloestase, Inhibitors, the membrane-type MMPs (MT-MMPs) and potential inducers. Fig. (2).

There are at least 18 distinct vertebrate MMPs. **(Gross and Lapiere, 1962 and (Barrett *et al.*, 1998).** Human MMPs are characterized by its dependable upon the presence of cofactor, ability to degrade ECM and specific evolutionary DNA sequences. The MMPs had high protein sequence domain structures

(Heikkilà, 2005).



Functional classification of MMPs.



Evolutionary classification.

(Massova *et al.*, 1998 and Shapiro , 1998 ; Hideaki *et al* ., 2001 ; Alali *et al* ., 2018 ;Ali *et al* .,2018; Barisic *et al* ., 2018 ; Hao ,2018 ; Marilena and Conor , 2018 ; Parente and Castro,2018 ; Pullen *et al* ., 2018 ; Rojas et al ., 2018; Zhou et al .,2018 ; Marcink *et al* ., 2019 ;Singh *et al* ., 2019 and Wu *et al* ., 2019).

MMPs inhibitors:

The MMPs are inhibited by endogenous tissue inhibitors of metalloproteinases (TIMPs) that consists of a family of four prostate inhibitors such as TIMP-1, TIMP-2, TIMP-3, and TIMP-4. Synthetic inhibitors generally contain a chelating agent that binds to the catalytic zinc atom at the MMPs activity site. Common chelating groups include hydroxamates, carboxylates, thiols, and phosphinyls. Hydroxymates are potent inhibitors of MMPs and other zinc-dependent enzymes, due to their ability to cheliate of the zinc atom **(Clark 2001; *Evrosimovska et al.*, 2011 and Matrix Metalloproteinases,2011).** MMPs and their inhibitors (TIMPs) implicated in many pathogenic cases such as idiopathic pulmonary fibrosis (IPF)depending upon cases reported an elevated levels of MMPs (including MMP-1,MMP-7 , MMP-8 and MMP-9) in blood or lung samples. Authors believed that MMP-9 is a novel therapeutic target for Influenza viral infection. MMP inhibitors shared in different biological conditions .Currently, doxycyclin is the only MMP inhibitors approved by FDA .MMP inhibitors

have been proposed as potential tools in the management of OA, CV diseases and cancer. The Tissue inhibitors of MMPs did the same action **(Hideaki *et al.*, 2001; Liu and Khalil, 2017).** MMPs and its tissue inhibitors (TIMP) gene considered as a predisposing players in human reproductive disorders **(Barisic *et al.*, 2018; Jasberg *et al.*, 2018).** The destructive effects of MMPs are inhibited by endogenous tissue inhibitors (TIMPs), through interface between host's by Tat (Transcription) protein of HIV and Bovine viral diarrhea (BVD) virus and ECM, which induced structural changes in the endothelial barriers by degrading ECM. **(Singh *et al.*, 2019).**

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