Matrix Metalloproteinases (MMP), a Major Responsible Downstream Signaling Molecule for Cellular Damage - A Review

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Rec date: Jul 11, 2016; Acc date: Sep 28, 2016; Pub date: Oct 03, 2016

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Abstract

Matrix metalloproteinase (MMPs) family members are well known signaling molecules. MMPs are involved in tissue remodeling and are affiliated with several pathological, pharmacological and physiological processes. In addition, these also facilitate other downstream pathways such as cellular inflammation. However, members of this family are being investigated in several diseases as a clinical marker. These proteins are often found responsible in the development of various dysfunctions such as cardiovascular, kidney, liver, and nervous system disorder. Evidences also suggest that MMPs take part in organ rejections during organ transplantations. Besides, MMPs also trigger accumulation of unnecessary immune cells which further exacerbate the situation resulting in a drug therapy failure. Furthermore, many harmful downstream kinases are induced by MMPs signaling. Therefore, it has been an imperative issue to establish a noble and alternative drug therapy against MMPs family for ensuring safety against several lives threatening phenomenon. This review will explain the molecular mechanism of MMP family members and few possible drug therapies modulating MMPs function.

Keywords: Cellular damage; Downstream molecules; Inflammation; Apoptosis; MMP

Abbreviations:

TRADD: TNFRSF1A-associated via death domain; FADD: Fas-associated protein with death domain; Rac1b: Alternative splicing of Rac1 generates Rac1b; BAX: BCL2-associated X protein; Bcl-2: B-cell lymphoma 2; CHEK2: Human gene checkpoint kinase 2; MDM2: Mouse double minute 2 homolog also known as E3 ubiquitin-protein ligase Mdm2; PERK: Protein kinase RNA-like endoplasmic reticulum kinase; ATF4: Activating transcription factor 4; APAF1: Apoptotic protease activating factor 1; IAP: The inhibitor of apoptosis

Introduction

Diabetes, obesity and hyperinsulinemia may lead to liver damage [1], heart dysfunctions [2] and end stage renal diseases [3]. Evidences also revealed that the rate of cancer development is also increased among patients throughout the world [4]. All together, the rate of mortality and morbidity due to metabolic diseases and cancer have been increased in an alarming rate [5]. In most of the cases, it was observed that downstream small molecules such as interleukin-1β, tumor necrosis factor-α, activator protein-1, hypoxia induced factor, macrophage inflammatory protein and nuclear factor-κB were found responsible for cellular damage and progression of multiple pathologic conditions [6]. Conversely, recent studies also showed that matrix metalloproteinase plays a significant role as a signaling molecules [7]. MMPs family has been identified for the development of several diseases [8] such as skin diseases [9], diabetic complications [10], atherosclerosis [11], end stage renal diseases [12], fibrosis [13], vascular dysfunctions [14], inflammation [15], chronic hepatic diseases [16], iron overload [17], pulmonary emphysema [18], cerebral ischemia [19], myocardial infarction [20], angiogenesis [21], cancer [22], apoptosis [23] and several other diseases.

Polymorphism in MMPs may promote alteration of several gene regulation that consequently change the genetic profile [24]. Similarly, it has been reported that smoking cigarettes may induce MMPs and in turn accelerates the development of several types of cancers [25]. One recent report evaluated that MMP-13 role in the development of atherosclerosis via AKT-ERK mediated pathway and explained the migration of vascular smooth muscle cells (VSMCs) [26]. Another study also investigated that neuronal matrix metalloproteinase-9 which showed that it may be responsible for several
neurodegenerative processes by activating ER stress in ALS motor neurons [27]. Expression of MMP-2/MMP-9 were also observed in experimental acute kidney allograft rejection [28]. The members of MMP family are also identified as pro-inflammatory signaling molecules in various studies [29]. In addition, MMPs are further responsible for regulation of several growth factors like VEGF and EGF which ultimately damage vascular system [30]. Furthermore, study also revealed that MMP-8 delays wound healing process in mice [31].

In the last three decades, experiments on this protein family have been largely investigated the multiple up-regulated and down-regulated pathways for cellular catabolism, production and renewal of various biochemical processes. As MMP family members are playing central role in multiple diseases progression, development and establishment of MMP inhibitors may have been a primary concern for the current ongoing research in this field. It has been noticed that doxycycline non-selectively suppresses MMP function in patients suffering abdominal aneurysm [32]. Over 60 other MMP inhibitors are currently being investigated to develop an active component against MMP mediated dysfunctions [33]. MMP inhibitors may play a beneficial role by abating several cellular signaling pathways like cellular inflammation, vascularization, fibrosis and apoptosis. Therefore, this review will evaluate the possible molecular mechanisms induced by MMP family members and few possible treatment approaches in various pathophysiological conditions.

Matrix Metalloproteinases and their Family Members

Generally, enzymes are known as catalysts which speed up a reaction. Thus, MMPs catalyze several pathways for cell migration, invasion, regulation and proliferation [34]. It was previously thought that MMPs are present in tissues to help degrading several regulatory components of the extracellular matrix and other basement membrane. However, recent studies explored that they may also play significant role as a prime regulator for various signaling networks. These proteins also have been known as the member of metzincin group of proteases which contribute to the conserved zinc-binding motif inside their catalytic binding sites [35]. MMPs are mainly triggered by several factors and chemicals such as oxidized glutathione, chaotropic agents, thiol-modifying agents, sodium dodecyl sulfate and free radicals which interfere with cysteine-Zn2+ of the cysteine-switch motif (Figure 1) [36].

Several members of MMP family also have been isolated. In 1962, the concept of MMP was first established [39], since then more than 30 active members of this family have been characterized successfully. Several sub-classes have been drawn for identification like MMP-1, MMP-8 and MMP-13 belong to collagenases subclass; MMP-2 and MMP-9 belong to gelatinases subclass; MMP-3, MMP-10 and MMP-11 belong to stromelysins subclass; MMP14, MMP-15 and MMP-17 belong to membrane-type MMPs; MMP-7 and MMP-26 belong to matrilysins subclass (Table 1) [40].

Table 1: An overview of MMP family members.
<table>
<thead>
<tr>
<th>Group</th>
<th>Protein name</th>
<th>Sub cellular location</th>
<th>Substrate(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collagenases</td>
<td>MMP1</td>
<td>Secreted</td>
<td>Collagen types I, II, III, VII, and X</td>
</tr>
<tr>
<td></td>
<td>MMP8</td>
<td>Cytoplasmic granules and secreted</td>
<td>Collagen types I, II, III, VII, and X</td>
</tr>
<tr>
<td></td>
<td>MMP13</td>
<td>Secreted</td>
<td>Collagen types I, II, III, VII, and X</td>
</tr>
<tr>
<td>Gelatinases</td>
<td>MMP2</td>
<td>Secreted, membrane, mitochondria, nucleus</td>
<td>Collagen types I, Collagen types I, II, III, VII, and X</td>
</tr>
<tr>
<td></td>
<td>MMP9</td>
<td>Secreted</td>
<td>Gelatin types I and V, Collagen types IV and V, and Fibronectin</td>
</tr>
<tr>
<td>Stromelysins</td>
<td>MMP3</td>
<td>Secreted</td>
<td>Gelatin types I, III, IV and V, Collagen types III, IV, IX and X, Laminin, Febronectin, pro-MMP1</td>
</tr>
<tr>
<td></td>
<td>MMP10</td>
<td>Secreted</td>
<td>Gelatin types I, III, IV and V, Collagen types III, IV, IX and X</td>
</tr>
<tr>
<td></td>
<td>MMP11</td>
<td>Secreted</td>
<td>α-1-antitrypsin</td>
</tr>
<tr>
<td>Matriylsin</td>
<td>MMP7</td>
<td>Secreted</td>
<td>Gelatin types I, III, IV and V, and Febronectin</td>
</tr>
<tr>
<td></td>
<td>MMP26</td>
<td>Secreted</td>
<td>Gelatin type I, Collagen type IV and Febronectin</td>
</tr>
<tr>
<td>Enamelysin</td>
<td>MMP20</td>
<td>Secreted</td>
<td>Aggrecan</td>
</tr>
<tr>
<td>Membrane-type (MT) MMPs</td>
<td>MMP12</td>
<td>Secreted</td>
<td>Elastin</td>
</tr>
<tr>
<td></td>
<td>MMP14</td>
<td>Membrane</td>
<td>Pro-MMP2</td>
</tr>
<tr>
<td></td>
<td>MMP15</td>
<td>Membrane</td>
<td>Pro-MMP2</td>
</tr>
<tr>
<td></td>
<td>MMP16</td>
<td>Membrane</td>
<td>Collagen type III and Febronectin</td>
</tr>
<tr>
<td></td>
<td>MMP17</td>
<td>Membrane</td>
<td>Fibrin</td>
</tr>
<tr>
<td></td>
<td>MMP24</td>
<td>Membrane</td>
<td>N-cadherin(CDH2)</td>
</tr>
<tr>
<td></td>
<td>MMP25</td>
<td>Membrane</td>
<td>Pro-MMP2</td>
</tr>
<tr>
<td>Others</td>
<td>MMP19</td>
<td>Secreted</td>
<td>Collagen type IV, Laminin, nidogen, Nascin-C isoform, Fibronectin, and type I gelatin.</td>
</tr>
<tr>
<td></td>
<td>MMP21</td>
<td>Secreted</td>
<td>α-1-antitrypsin</td>
</tr>
<tr>
<td></td>
<td>MMP23</td>
<td>Cell membrane, ER membrane</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>MMP27</td>
<td>ER membrane</td>
<td>Fibronectin, Laminin, Gelatins and Collagens</td>
</tr>
<tr>
<td></td>
<td>MMP28</td>
<td>Secreted</td>
<td>-</td>
</tr>
</tbody>
</table>

Matrix Metalloproteinases and Inflammation

Inflammation is the signaling process for a cellular regulation which denotes imbalance inside organ or tissue. Pain, swelling, redness or rash and fever are generally observed in acute cases of inflammation but often noticed cellular death if the process persists for a longer period of time [3,41,42]. Furthermore, MMP family members are also known as inflammatory cytokines [43]. The outcomes of inflammation were cell necrosis, damage and cellular death in various animal model studies [44,45].

It has been noticed that MMP-9 is highly responsible molecule in neuro-degenerative diseases which further inducing the activation of pro-inflammatory factors such as PKCs, ROS, ERK1/2, PI3K/Akt, NF-κB, and AP-1 (Figure 2) [46]. Several experiments also noticed that MMP-1 stimulates VEGFR2 expression which further promotes endothelial proliferation via activation of NF-κB and protease activated receptor-1 (PAR-1) [47,48].

In rodents, MMP-2 and MMP-9 significantly increased inflammatory cytokines such as TNF-α, IL-6, IL-8, IL-1β, MIP-1α and GROα in the lung when the animals were treated with LPS. This study also revealed that LPS administration increased tissue MPO, neutrophil, and eosinophils level in lung [49]. Studies also suggested that family members of MMP regulate chemokines activities. The mechanism of controlling chemokines has been explained as the cleavage progressed by MMPs [50,51].

Another study has demonstrated that MMP-2 directly cleavages motif of monocyte-chemotactic protein (MCP) in a yeast two-hybrid system which is further known as CCI7 or MCP3 [52]. Other studies also explored that MMP-7 plays as a potent pro-inflammatory cytokines in lung. Accumulation of neutrophil reflux and oxidative burst cause activation and production of mucosal immunity along with epithelial migration that eventually possess mortal damage [52,53].
Matrix Metalloproteinases to Induce Cytokines Production

MMPs not only stimulate immune cells but also induce several other cytokines production and activation. Evidences have suggested that MMP-2 activates c-Jun N-terminal kinase (JNK), and p38 mitogen-activated protein kinase (p38 MAPK) which further activates transcription factor for NF-κB in rat HSCs [54]. The expression of MT1-MMP and proMMP-2 were also noticed in tumor cells [55]. Iron is generally stored inside a cell and highly regulated by hemeoxygenase (HO) [41]. In several disease conditions, hemeoxygenase is degraded and resulting in iron overload which further assists in the development of multiple pathogenesis [56]. MMP-1, MMP-2 and MMP-8 have strongly been blamed to degrade the HO regulation which initiate iron deposition [57,58]. Previous investigation also suggested that expression of MMP-2 and MMP-9 may increase the production of HLA-DR antigens concentration on plaques by interacting with COX-2/mPGES [59]. Another experiment found that MMP-9 helps in the expression of hematopoietic CD34+/CXCR4+ stem cells that is linked to wound healing capability [7].

Matrix Metalloproteinases and Apoptosis

Apoptosis is a biological phenomenon where cells generally are programmed to die without inducing inflammation. Sometimes body initiates this process to replace old cells. This process can be harmful when a hazardous molecule invades inside a biological system and starts apoptosis where it is not necessary [60]. MMPs family members have been intensively blamed to initiate this process which results in cellular death [61]. It is mostly suggested and evaluated that the process of apoptosis is taken through the production of caspase proteins [62]. A possible mechanism has been proposed for apoptosis via MMP in Figure 3. Generation of free radicals, along with up regulation of MMP-9 from BK-challenged brain astrocytes trigger brain cell apoptosis. This study also suggests that MMP-9 mediated pathway may severely damage neural cell [63]. N-cadherin, a cell survival protein was found less due to MMP-7 expression on human atherosclerotic plaques which ultimately reduces the cell survival rate [64]. Other study also observed that MMP mediated cerebral endothelial cell death may occur due to over expression of caspase activity [65].

Matrix Metalloproteinases and Cancer

Cancer is a group of various metabolic disorders which explains abnormal or uncontrolled cell proliferation that may spread to several other organs [66]. In the recent year smoking cigarette, consumption of alcoholic beverages and chewing tobacco have been identified as the main reasons for the development of cancer [67]. Less or no physical activity, taking
high fructose containing beverages, environmental exposure, viruses like hepatitis C or HPV and genetic predisposition also play major role in cancer which may lead to death globally [68]. According to American Cancer Society, 589,430 people died of cancer and 1,658,370 new people were diagnosed with cancer in USA in the year 2015 [66]. It is also projected that this figure would be around 22 million in 2030 and the treatment cost will be out of reach to the poor and middle class people [69]. The total cost of cancer treatment and management were estimated more than 1.6 trillion US dollars globally in 2010 [70].

The relationship between cancer and MMP is very strong. Several studies have been investigated that the expression of MMP family members found high in the cancer subjects [71,72]. The expression of MMP-2 and MMP-9 have been targeted in the primary stage of colorectal cancer in mice [73]. Similarly, Membrane type 1-matrix metalloproteinase (MT1-MMP, MMP-14) is also co-related with cancer invasion and metastasis. This investigation suggests that MMP may trigger TGF-β that further induce CUTL1 and subsequently, of Wnt5a through paracrine mediated mechanisms [74]. MMP-9 also has been identified in tumor invasion and metastatic diffusion, including bone marrow and can be found in brain cancer and targeted as a potential biomarker for breast cancer [75]. Furthermore, MMP mediated cancer is generally initiated through inflammatory cytokines [76].

Possible Treatment Approaches

Evidences suggested that the treatments of several diseases are getting difficult due to interfering role by MMP family members. Inhibiting MMP can be a good approach to reduce several pathogenesis like chronic inflammation and cancer [77]. Both natural and synthetic components are being aggressively focused against MMP family members [78]. Zn£±-chelating hydroxamate has been observed effective in the development of MMP inhibitors as this carries superior ΔG values. This helps to bind around Zn2+- [79,80]. Signaling molecules such as MAPK or p38MAPK have been found responsible in many diseases. So, blockage of these kinases can be a good way to fight against such pathogenesis [6]. Natural product like naringen down regulated MMP-2 and MMP-9 by reducing signaling of MAPK in Human glioblastoma cell lines (Table 2) [81]. Another study exposed inhibitory activity of MMP-3 by reducing PI3K-Akt signaling pathway when the cell was treated with resveratrol [82]. Gallic acid, a very potent antioxidant observed effective in oral cancer by mainly reducing FAK, PKC, RhoA and NF-κB [83]. Kaempferol, another phenolic acid, reduced c-Jun activity and phosphorylation of ERK1/2 expression by controlling MMP-2 in human tongue squamous carcinoma cell line [84].

Similarly, synthetic molecules have also shown good activity against MMP family. DX-2400, a synthetic component which showed inhibiting activity of MMPs in HT-1080 cells line by attenuating proMMP-2 level [85]. More than 50 chemical compounds are in the clinical trials, although the first clinical trial of MMP inhibitor against cancer was a failure [86]. Many of the MMP inhibitors found not ideal, metabolically unstable, less oral bioavailable and show unwanted side effects. The inhibitory effects of MMP inhibitors were observed well in animal models. However, they were found disappointed when used in small clinical trial due to presence of other diseases in the volunteers. As MMP is basically regulated by TIMP, inhibitors of TIMP can also be a good choice. Previous study found that using TIMP inhibitor (TIMP-1,2,3 and 4) on the catalytic site of MMP might not provide good activity because TIMPs always differ in their affinity for specific MMP family members [86]. However, no drug is hundred percent specific, potent and may often exert side effects. Using proper evaluation, docking, structure activity relationship and large clinical trials might bring a good molecule to treat the diseases like inflammation or cancer.

<table>
<thead>
<tr>
<th>Name of Molecule</th>
<th>Model</th>
<th>Mechanism</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cordycepin</td>
<td>Rat aortic smooth muscle cells</td>
<td>Inhibits MMP-13 by blocking migration of vascular smooth muscle cells by preventing Akt and ERK-dependent regulation</td>
<td>[87]</td>
</tr>
<tr>
<td>Naringin</td>
<td>Human glioblastoma cell lines U87</td>
<td>Down-regulates the expression of MMP-2, MMP-9 by attenuating the MAPK signaling pathways including ERK, JNK and p38</td>
<td>[81]</td>
</tr>
<tr>
<td>DX-2400</td>
<td>HT-1080 cells</td>
<td>Blocks MMPs expression by inhibiting proMMP-2 processing</td>
<td>[85]</td>
</tr>
<tr>
<td>Ac-LEHD-cmk,</td>
<td>Neonatal cardiomyocytes</td>
<td>Blocks the MMP-2 activity by reducing Tnl proteolysis and hypoxia-reoxygenation</td>
<td>[88]</td>
</tr>
<tr>
<td>Fisetin</td>
<td>Male C57BL/6 mice</td>
<td>Blocks pro-MMP-2 and active MMP-2 activity</td>
<td>[89]</td>
</tr>
<tr>
<td>Solamargine</td>
<td>HepG2 cells</td>
<td>ReducesProMMP-2 and ProMMP-9 levels in the cytosol thus blocks the expression of MMPs</td>
<td>[90]</td>
</tr>
<tr>
<td>Caffeic acid phenethyl ester</td>
<td>SCC-9 oral cancer cells</td>
<td>Inhibits MMP-2 expression by up regulation of tissue inhibitor of metalloproteinase-2 (TIMP-2), reducing focal adhesion kinase (FAK) phosphorylation and by the activation of p38/MAPK and JNK</td>
<td>[91]</td>
</tr>
<tr>
<td>linoleic acid to α-linolenic acid</td>
<td>Sprague-Dawley rats and Human chondrocytes</td>
<td>Inhibits MMP-13 expressions by blocking the IL-1 mediated stimulation</td>
<td>[92]</td>
</tr>
<tr>
<td>Nobiletin</td>
<td>UZOS and</td>
<td>Down regulates MMP-2 and MMP-9 expressions via ERK and JNK pathways and by inactivating NF-κB, CREB, and SP-1</td>
<td>[93]</td>
</tr>
<tr>
<td>Compound</td>
<td>Cells Tested</td>
<td>Mechanism</td>
<td>References</td>
</tr>
<tr>
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</tr>
<tr>
<td>Resveratrol</td>
<td>HOS cells, RA FLS cells</td>
<td>Blocks MMP-3 by inhibiting of PI3K-Akt signaling pathway</td>
<td>[82]</td>
</tr>
<tr>
<td>Quercetin</td>
<td>U87-MG glioblastoma and U251 and SHG44 glioma cell lines</td>
<td>Reduces MMP-9 by blocking the Ras/MAPK/ERK and PI3K/AKT pathways</td>
<td>[94]</td>
</tr>
<tr>
<td>Kaempferol</td>
<td>Human tongue squamous cell carcinoma SCC4 cells</td>
<td>Inhibits MMP-2 expression by inhibiting c-Jun activity and phosphorylation of ERK1/2</td>
<td>[84]</td>
</tr>
<tr>
<td>Naringenin</td>
<td>Human prostate cancer cells</td>
<td>Reduces the expression of MMPs by inhibiting ERK1/2 and the levels of reactive oxygen species (ROS)</td>
<td>[95]</td>
</tr>
<tr>
<td>Diallyl Sulfide, Diallyl Disulfide, and Diallyl Trisulfide</td>
<td>Human Colon Cancer Cells</td>
<td>Inhibits MMP by down-regulating the expression of PI3K, Ras, MEKK3, M KK7, ERK1/2, JNK1/2, and p38</td>
<td>[96]</td>
</tr>
<tr>
<td>Epigallocatechin-3-gallate (EGCG)</td>
<td>RA FLS cells</td>
<td>Inhibits MMP-1 and MMP-13 by blocking RANTES/CCL5 expression and phosphorylation of JNK p46</td>
<td>[97]</td>
</tr>
<tr>
<td>Luteolin</td>
<td>A431-IIICancer Cells</td>
<td>Suppresses MMP secretion by attenuating the phosphorylation of cortactin and Src</td>
<td>[93]</td>
</tr>
<tr>
<td>Gallic acid</td>
<td>Human oral cancer cells</td>
<td>Inhibits MMPs by reducing FAK, MEKK3, PERK, p-p38, p-JNK1/2, p-ERK1/2, SOS1, RhoA, Ras, PKC, p-AKT(Thr308), PI3K, NF-κB p65</td>
<td>[83]</td>
</tr>
</tbody>
</table>

**Limitations of MMP Inhibitors**

Understanding the characteristics, structure, domain and function of these key enzymes may have significant applications for several drug therapies like cancer and auto immune diseases. Since last 2 decades, explorations on MMP inhibitors are largely evaluated to introduce a new and effective molecule. Several inhibitor have been applied against MMP proteomase but due to having Zn2+ binding domain, many good molecules failed to achieve their activity [98]. Monoclonal antibody has been also proposed against MMP domain and found quite effective but those proteins were never applied further due to having much supporting data [85].

Figure 4: A represents - general structure of the matrix metalloproteinases (MMPs). It contains a signal peptide, a pro-peptide domain, a catalytic domain with a highly conserved zinc-binding site, and a hemopexin-like domain linked to the catalytic domain by a hinge region.

In case of MMP-2 and MMP-9, they contain fibronectin type II inserts within the catalytic domain. The membrane-type MMPs (MT-MMPs) carry a transmembrane domain at the C-terminal end of the hemopexin-like domain. The hemopoxin domain is absent in MMP7. B represents - basic domain structure of human matrix metalloproteinase 2 (MMP2). The image were processed using PyMol(The PyMOL Molecular Graphics System, Version 1.8 Schrödinger, LLC.) and UCSF Chimera package. Inspired from [37,38,99].

**Future Direction and Conclusion**

In conclusion, our literature review suggests that the MMPs are playing a significant role in the regulation of many cell types. Most of them are also associated with cellular damage and disease induction. So, measurement of MMPs in various diseases can be used positively to evaluate pathophysiologic condition. Thus, MMP inhibitors can serve as potential drug candidate against many diseases.

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