REVIEW

Pleiotropic Roles of Metalloproteinases in Hematological Malignancies: an Update

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Abstract

Controlled remodeling of the extracellular matrix (ECM) is essential for cell growth, invasion and metastasis. Matrix metalloproteinases (MMPs) are a family of secreted, zinc-dependent endopeptidases capable of degradation of ECM components. The expression and activity of MMPs in a variety of human cancers have been intensively studied. They play important roles at different steps of malignant tumor formation and have central significance in embryogenesis, tissue remodeling, inflammation, angiogenesis and metastasis. However, increasing evidence demonstrates that MMPs are involved earlier in tumorigenesis. Recent studies also suggest that MMPs play complex roles in tumor progression. MMPs and membrane type (MT)-MMPs are potentially significant therapeutic targets in many cancers, so that designing of specific MMP inhibitors would be helpful for clinical trials. Here, we review the pleiotropic roles of the MMP system in hematological malignancies *in-vitro* and *in-vivo* models.

Keywords: Matrix metalloproteinases - tumorigenesis - MMP inhibitors - leukemias

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Introduction

Matrix metalloproteinases (MMPs) are a family of zinc dependent endopeptidases that have the capability to breakdown all the connective tissue (Nagase et al., 2006). Over the past decades, noteworthy advances have been reported in MMP research worldwide. These have included a better understanding of the biochemistry of these zinc dependent enzymes in terms of their activation, regulation and substrate specificity. Their expression is known to enhance in various inflammatory, malignant and degenerative diseases. Elevating the possibility that inhibitors of MMPs may possess therapeutic potential. For the development of MMPIs drugs their structure was identified by X-ray crystallography and nuclear magnetic resonance spectroscopy (NMR). The new challenge in MMP research is to understand the complex role these enzymes in human diseases and to design inhibitors that will be useful for treatment.

MMPs play important roles in multiple physiological and pathological processes which participates in the development of the embryo, inflammation, wound healing, angiogenesis, immunity, tumor invasion and metastasis (Chaudhary et al., 2013). The expression levels of MMPs are increased in almost every type of human cancer and it correlates with different stages of solid tumor. The clinical data also strongly support the participation of MMPs in the invasion, metastasis and, progression of different types of human cancer (Chaudhary et al., 2011; Gao et al., 2014; Hwang et al., 2014; Roy et al., 2014).

Many recent studies have shown that cancer invasion and metastasis progresses through the involvement of loss of cell-cell interaction, cell-matrix adhesion, extracellular matrix degradation (Zhang et al., 2014). Physiologically, tumor angiogenesis promotes certain stage of tumor progression and beginning of tumor angiogenesis has been defined as an angiogenic switch (Hanahan et al., 1996). The polymorphic association, expression and activity of MMPs in a variety of human cancers have been well defined. MMPs have been chosen as promising targets for cancer therapy on the basis of their aberrant up-regulation in malignant tumor formation and their capability to stimulate cancer metastasis (Hua et al., 2011).

The purpose of this review is not only to provide role of MMPs and their inhibitors but, also give an overview of what is the current status and pleiotropic roles of MMPs system and tumor-induced metastasis and angiogenesis. Also in this review we will focused on the current status of development of MMPs drugs for the cure of solid and hematological malignancies.

Stimulation of MMPs in the Potentially Malignant and Malignant Tumors

MMPs have been divided into distinct subclasses: collagenases (MMP-1, MMP-8, MMP-13, and MMP-18), gelatinases (MMP-2, MMP-9), stromelysins (MMP-3, MMP- 10 and MMP-11) and matrilysins (MMP-7, MMP-

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26) and other MMPs (Chaudhary et al., 2010). Most of the MMPs are inhibited by specific endogenous tissue inhibitor which is known as tissue inhibitors of matrix metalloproteinase [TIMPs] Figure 1. Which comprises as family of four protease inhibitors known as TIMP-1, TIMP-2, TIMP-3 and TIMP-4, these four human TIMPs have fully cloned and sequenced in human. Among them, TIMP-1 and TIMP-2 are secreted in soluble form by a wide range of cell types, including fibroblasts, monocytes or macrophages (DeClerck et al., 1992). The role and expression of MMPs and tissue inhibitors of matrix metalloproteinases (TIMPs) in solid malignancies are well established but in case of haematological malignancies there is few data available. There is no much data available on role of MMPs and its inhibitors in hematological malignancies with respect to their expressions and polymorphic association. Therefore, it is difficult to find a suitable drug targets therapy for the treatment. The role of ECM-degrading enzymes, which are mainly produced by haemopoietic and stromal cells within the bone marrow microenvironment, are not well understood.

An imbalance between the cell proliferation and apoptosis causes tumour growth. It is influenced by angiogenesis, cell to cell as well as cell to ECM interactions. ECM consists of proteins and polysaccharides distributed in many different tissues of the body. ECM environment provides appropriate conditions for cell growth, cell differentiation and survival of tissues. It constitutes fibrous proteins such as collagen and elastin and elongated glycoprotein such as fibronectin and laminin, which provide cell matrix adhesion. The hematopoietic microenvironment is composed of cells of the hematopoietic and non-hematopoietic origins. These cellular components produce soluble and membrane-bound cytokines as well as ECM (Vu et al., 1998).

In BM hematopoietic microenvironment, ECM is mainly made up of collagens (type I, III, IV, V), laminin, vitronectin, thrombospondin, fibronectin proteoglycans and glycosaminoglycans (Olczyk et al., 2014). MMPs participate in the turnover of ECM in the hematopoietic microenvironment and it regulates the release of HSCs and mature leukocytes from BM into peripheral blood (PB) (Chaudhary et al., 2013). The normal physiological process of the hematopoiesis, proliferation, differentiation and migration of the hematopoietic stem cells (HSCs), is regulated by the immune system (Riether et al., 2015). Recently, reported that that Matrix metalloproteinase plays important role in stem cell mobilization (Klein et al., 2015). MMPs are potent triggers and contributors of the angiogenic switch, blocking MMPs at the site of tumor development would substantially inhibit angiogenesis and will also disrupt already established angiogenic networks (Deryugina et al., 2010). The term vasculogenic mimicry (VC) describes the formation of fluid-conducting channels by highly invasive and genetically dysregulated tumor cells. Two distinctive types of vasculogenic mimicry have been described. Vasculogenic mimicry of the tubular type may be confused morphologically with endothelial cell-lined blood vessels. Vasculogenic mimicry of the patterned matrix type have matrix proteins such as laminin, heparan sulfate proteoglycan, and collagens IV and VI. Lu et al did the experiment to know the underlying mechanisms of VM in gallbladder carcinomas via the 3-D matrix in-vitro, and in-vivo by using nude mouse xenografts and concluded that PI3K/MMPs/Ln-5γ2 and EphA2/FAK/Paxillin signaling pathways contribute to tumor growth and vasculogenic mimicry of gallbladder carcinomas (Lu et al., 2013).

In the breast cancer increased expression of thioredoxin (Trx)-1 and matrix metalloproteinase (MMP)-9 was associated with malignant cancer progression. Trx-1 overexpression stimulated MMP-9 expression, de-regulated the MMP-9/TIMP-1 equilibrium and augmented MMP-9 involvement in a more invasive phenotype. Farina et al provided a functional basis for Trx-1 and MMP-9 association in malignant breast cancer and identified Trx-1 and NF-κB as potential targets for reducing involvement of MMP-9 in malignant behavior (Farina et al., 2011).

Hence it suggests that in the hematological and solid malignancies, MMPs participates in stimulation of tumorigenic and invasiveness function.

Pathological and Cellular Establishment of MMPs in Hematological Malignancy

Fanconi anemia (FA)

Fanconi anemia (FA) is an inherited (autosomal recessive) bone marrow failure syndrome characterized by a variable number of developmental abnormalities, genomic instability, hypersensitivity to DNA crosslinking agents and an increased predisposition to malignancy. It is genetically heterogeneous, with 13 subtypes/complementation groups (FA-A, FA-B, FA-C, FA-D1, FA-D2, FA-E, FA-F, FA-G, FA-I, FA-J, FA-L, FA-M, and FA-N). The genes responsible for these subtypes (FANCA, FANCB, FANCC, FANCD1, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCJ, FANCL, FANCM, and FANCN, respectively) have all been identified (Bagby et al., 2006). Mutation (16 FA genes) which participates in the FA-BRCA DNA repair pathway has been characterized by an overproduction of many cytokines, MAPKs, Interleukins and MMPs. The overexpression of additional secretory factors such as IL-6, IL-8, MMP-2, and MMP-9 in FA cells and in cells depleted of FANCA or FANCC proved that their expression is under the control of NF-κB/TNF-α signaling pathways (Epanchintsev et al., 2014). ROMO1 gene who regulates Redox states serve as an inducer of NF-kB-driven EMT factors in FA (Shyamsunder et al., 2015). Epanchintsev et al demonstrated that these overexpressed secretory factors were effective in promoting the cell proliferation, migration, and invasion of surrounding malignant cells and participate in the process of epithelial mesenchymal transition (EMT) .They also modulated the expression of EMT markers such as E-cadherin and SNAIL. Overall these data suggested that the upregulation of EMT promoting factors in FA may contribute to predisposing FA patients to cancer, thus provides new visions for therapeutic drug targets for FA (Epanchintsev et al., 2014).

Roomi et al investigated effects of a nutrient mixture (NM) containing, ascorbic acid, lysine, proline and green tea extract on Fanconi Anemia human fibroblast

cell lines FA-A:PD20 and FA-A:PD220 on matrix metalloproteinase expression, invasion, cell proliferation, morphology and, apoptosis (Roomi et al., 2013). They concluded that the nutrient mixture inhibited matrix metalloproteinase expression, invasion in FANCA and induced toxicity in FANCC lymphoblasts. These results suggested that the nutrient mixture may have therapeutic potential in Fanconi Anemia associated neoplasia. (Roomi et al., 2014). Revera et al. (2015) evaluated the overall involvement of metalloproteinase activity in FANCA cells by exposing them to the antioxidants N-acetyl cysteine (NAC) and resveratrol (RV) and concluded that treatment of Fanconi anemia patients with antioxidants may be important in FA therapy (Revera et al., 2015).

Myelodysplastic syndromes (MDS)

Myelodysplastic syndromes (MDS) are a heterogeneous group of neoplastic clonal stem cell malignancies. It is clinically present as anemia, leucopenia, thrombocytopenia and ineffective bone marrow hematopoiesis. It can be categorized into subtypes according to histological, and prognostic scoring systems have been proposed. Several of these systems have gained acceptance with the French-American-British (FAB) classification as modified by the World Health Organization (WHO), the International Prognostic Scoring System (IPSS). According to WHO classification MDS has been classified as Refractory cytopenias with unilineage dysplasia (RCUD), refractory anemia (RA), refractory neutropenia (RN), refractory thrombocytopenia (RT), Refractory anemia with ring sideroblasts (RARS), Refractory cytopenias with multilineage dysplasia (RCMD), Refractory anemia with excess blasts, type 1(RAEB-1), Refractory anemia with excess blasts, type 2 (RAEB-2), MDS associated with isolated del(5q) Del(5q), Childhood MDS, including refractory cytopenia of childhood (RCC), MDS, unclassifiable (MDS-U). Clinically, MDS presents with anemia, infections due to neutropenia, bleeding tendencies due to thrombocytopenia. Many others environmental factor such as pesticides, cigarette/bidi smoking, radiation, chemotherapy and exposure to benzene may increase susceptibility of MDS (Vundinti et al 2009). MDS transforms to acute myeloid leukemia (AML) in approximately 10- 40% of cases. Survival following a diagnosis of MDS varies from a few months to more than ten years (comparable to age/sex matched normal populations) (Greenberg et al., 2002; List et al., 2004).

In most cases the cause of MDS is unknown. This is called primary MDS. Exposure to radiotherapy or chemotherapy can cause mutations that may lead to MDS. This is known as secondary or treatment-related MDS. Recently, Tong et al have done meta-analysis of the relationship between cigarette smoking and incidence of myelodysplastic syndromes and reported that smoking increases the risk of developing MDS and also demonstrated positive association between cigarette smoking and risk of MDS, and suggested that it occurs in a dose-dependent manner (Tong et al., 2013). Trisomy at chromosome number 8 is most frequent trisomy in MDS and AML. Monosomy at chromosome number 7 is most frequent chromosome aberration of MDS in childhood (Vundinti et al., 2009). Deletions of the long arm of the chromosome 5 (5q) are associated with good prognosis. Many other factors may be responsible for the development of MDS in older age and childhood MDS. MMPs may also contribute in the development of MDS because several studied represent mature leukocytes, such as neutrophil granulocytes, monocytes, macrophages and T lymphocytes are potent producers of MMP-2 and MMP-9 (Owen et al., 2003). The gelatinase production is thought to enable leukocytes to cross ECM barrier to reach their target tissue at the sites of inflammation. MMPs are a family of zinc-dependent proteolytic enzymes with a key role in cancer, including acute leukemia (Egeblad et al., 2002, Fanjul et al., 2010). Through cleavage of a wide variety of substrates, including almost all components of the ECM and different types of cytokines and chemokines, regulate migration of cells across the ECM, cell growth, angiogenesis and apoptosis. All these processes are essential for the dissemination of neoplastic cells.

There is paucity of data on role of MMPs in MDS. Ries et al studied the MMP production by bone marrow mononuclear cells from myelodysplastic syndrome and showed that in MDS, MMP-2 was found in three of eight (38%) of the patients, two of them undergoing progression of disease within 12 months (Ries et al., 1999). The study of Iwata et al showed that MMP-9 levels in freshly isolated blood monocytes did not correlate with any clinical parameters of MDS (Iwata et al., 2007). Yamaguchi et al suggested that increased collagenase activity may be an independent prognostic factor for the susceptibility to severe infection in MDS (Yamaguchi et al., 2005).

Based on the drug targets therapy, Bernal et al analyzed the effect of different concentrations of azacitidine drugs in two well-established MDS-derived acute myeloid leukemic cell lines: MOLM-13 and SKM-1 and reported that MMP9 expression and cell invasiveness increase during different concentration of azacitidine treatment and concluded that azacitidine increases MMP9 expression and enhances the invasiveness in-vitro assay (Bernal et al., 2013).

Acute myeloid leukemia (AML)

Acute myeloid leukemia is a clonal hematopoietic disorder that may be derived from either a hematopoietic stem cell or a lineage specific progenitor cell. AML is characterized both by predominance of immature forms and loss of normal hematopoiesis. Single or multiple hematopoietic lineages may comprise the leukemic clone. The successful diagnosis of acute myeloid leukemia (AML) has never been an easy task for the practicing pathologist. In AML the requisite blast/blast equivalent percentage is 20% in the peripheral blood and bone marrow; a lower percentage is acceptable in cases with AML-defining translocations and in acute erythroid leukemia. AML can occur in patients of any age, but in general, both the overall incidence and the proportion of total acute leukemias that are myeloid increase with age. The age-adjusted incidence of AML in the United States is 3.4 cases per 100,000 persons (Deschler et al., 2006). In general, AML arises due to inherited genetic mechanisms, environmental influences, specific

translocations, mutations and other genetic alterations. Core binding factor (CBF) AML includes AML with t (8; 21) and AML with inv (16)/t (16; 16) chromosomal abnormality. The Core binding factor (CBF) genes involved are RUNX1 (21q22, aka AML1, CBFA2) and CBFB (16q22). As part of the CBF heterodimer transcription factor complex, RUNX1 binds to DNA promoter sequences of genes needed for hematopoiesis, while CBFB protects the complex from proteolysis. Such selected regulation provides an important molecular mechanism for the dysregulation of gene expression during cancer development. (Okumura et al., 2008). Matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) were demonstrated to have important implications in the progression and invasiveness of many malignant disorders. In contrast, the biological significance of these molecules in human leukaemias is not clear. Li et al studied MMP and TIMP levels in AML and ALL patients and conclude that the level of marrow MMP-9 may be a useful surrogate marker for monitoring disease status in AML and propose it as a potential prognostic factor (Li et al., 2002). Altered epigenetic regulation is a recurrent theme in AML and over the last 5-10 years a greater understanding of the processes underlying this has led to the identification of multiple rational therapeutic targets (Gallipoli et al., 2015).

Acute lymphoblastic leukaemia (ALL)

Acute lymphoblastic leukaemia (ALL) comprises of neoplastic precursor cells committed to the B or T cell lineages. B-lineage ALL is more frequent, accounting for 85% of childhood ALL and 75% of adult ALL. Cytogenetic abnormalities are seen in the leukaemic clone in the majority of cases of B-ALL and often define specific entities with unique haematological and prognostic features (Campo et al., 2008). In childhood B-cell ALL, the ploidy of the leukaemic cells is a well-established prognostic factor. The most significant genetic determinants in paediatric ALL are t(9;22)(q34;q11) Philadelphia translocation, MLL rearrangements - particularly translocation t(4;11)(q21;q23), ETV6-RUNX1 fusion, iAMP21, t(17;19)(q22;p13) (Harrison et al., 2010). For T-lineage ALL, an abnormal karyotype is typically reported in 50-70% of cases and numerical abnormalities are less frequent than in B-cell ALL, with the exception of around 5% cases showing tetraploidy. Approximately 35% of cases show rearrangements involving the TCR loci at 7q34 (TCRB) or 14q11 (TCRA/D) (Graux et al 2006). Pan et al carried out a study to investigate the expression and clinical significance of MMP-2 and MMP-9 in patients with B-acute lymphoblastic leukemia (B-ALL). They concluded that MMP-2 and MMP-9 may be secreted by B lymphoblasts and may involve in the extramedullary infiltration. MMP-9 may correlate with poor prognosis (Pan et al., 2014).

It is known that leukemia patients with extramedullary infiltration (EMI) have a worse prognosis. The frequency of extramedullary infiltration (EMI) in acute myeloblastic leukemia (AML) is reported up to 40% and most prevalent in myelo-monoblastic and monoblastic subtypes of AML. Recent data showed that amyloid precursor protein (APP) is a ubiquitously expressed cell surface protein and it involved in mediating cell-cell or cell-matrix interactions. It also indicated involvement of the amyloid precursor protein in cell adhesion, motility, and proliferation (Jiang et al., 2013). Yang et al reported that the amyloid precursor protein was over expressed in papillary thyroid carcinoma (PTC) and high APP expression was associated with high malignant potential. Therefore, APP may serve as a prognostic marker and potential novel therapeutic target in PTC (Yang et al., 2012). The expression of APP and its prognostic significance in acute myeloid leukemia (AML) have not been well studied till date. Jiang et al studied that over expression of APP in acute myeloid leukemia (AML) enhances extramedullary infiltration (EMI) by MMP-2 and provides a novel clue that APP is involved in the EMI of leukemia by MMP-2 (Jiang et al., 2013).To explore mechanism underlying EMI, Wang et al analyzed SHI-1 cells, a highly invasive human acute monocytic leukemia cell line, and reported strong expression of MMP-2, membrane type 1 MMP (MT1-MMP) and TIMP-2. SHI-1 cells showed higher invasive ability to traverse reconstituted basement membranes (Matrigel) and stronger activation of proMMP-2 than other leukemia cell line such as NB4, K562, U937 and THP-1 cells. (Wang et al., 2010). Travaglino et al showed abnormal MMP expression in AML. They reported that production and release of MMP-2 and MMP-9 enzymes may influence haematopoietic cell behaviour and may provide a useful tool for diagnosis, prognosis and a possible target for experimental treatments (Travaglino et al., 2008). Kuittinen et al studied the expression of gelatinase-A (MMP-2) and gelatinase-B (MMP-9) in bone marrow aspirates from ALL patients and suggested that the gelatinase activity could be related with increased extravasation of the leukemic cells in ALL. They concluded that gelatinase A and B (MMP-2, MMP-9) in leukaemia and MMP-2 in AML may indicate a good prognosis markers. (Kuittinen et al., 2001). He et al carried out a study to investigate the mRNA and protein expression of CTGF, CYR61, VEGF-C and VEGFR-2 in bone marrow of patients with leukemia, and tried to analyze the role and clinical significance of these 4 factors in genesis and development of leukemia, infiltration and metastasis of leukemic cells. They concluded that these 4 factors mRNA and protein play a role in acute leukemia. Joint block of these angiogenesis-related factors may play an important role in targeting treatment of leukemia (He et al., 2014).

Childhood acute lymphoblastic leukemia (ALL) is characterized by its capacity to infiltrate different organs. Role of MMPs and TIMPs in acute lymphoblastic leukemia (ALL) has been reported. Scrideli et al evaluated the mRNA expression profile of TIMP-1, TIMP-2, MMP-2 and MMP-9 genes in diagnostic bone marrow samples and reported significant association between higher expression levels of MMP9 ,TIMP-2 and MMP-2 with T-ALL (Scrideli et al 2010). Schneider et al suggested that secretion of MMP-9 is an independent prognostic factor in childhood B-ALL. (Schneider et al., 2010). Leukemic cells express several members of the VEGF family and MMPs. On the basis of this background, Poyer et al reported that

autocrine VEGF-induced secretion of MMP-2/-9 in the physiopathology of childhood ALL (Poyere et al., 2009). Suminoe et al showed that mRNA contents of MMP-2 and MMP-9 were not associated with any ALL patient clinical characteristics. Only, positive correlation was found between hepatosplenomegaly and finally, suggested that MMP/TIMP balance is closely related to the infiltration of leukemia cells into extramedullary organs (Suminoe et al 2007). Pegahi et al reported that basal receptors and cytokines receptors (SDF-1, GM-CSF, bFGF, VEGF) stimulated secretions of gelatinases 2 and 9, and concluded that cytokine evoked production of MMPs in childhood acute lymphoblastic leukaemia (Pegahi et al., 2005). Kuittinen et al also supported that gelatinase activity could be related with increased extravasations of the leukemic cells in acute lymphatic leukemia (Kuittinen et al., 2001).

Chronic myelogenous leukemia (CML)

Chronic myelogenous leukemia (CML) are caused by expression of Bcr-Abl, a fusion gene generated by reciprocal t (9; 22) (q34; q11) chromosome translocation. Bcr-Abl-positive leukemias are characterized by premature release of myeloid and lymphoid lineage cells from BM, followed by expansion of these unhealthy cells in the peripheral blood (PB) and also infiltration of different organs such as liver, lung and spleen. The progression of CML cells involves not only accelerated cell proliferation and enhanced cell survival, but also increased cell motility and active invasion of leukemic cells through blood vessel and matrix barriers. Membrane-type 1 matrix metalloproteinase (MT1-MMP) is a member of transmembrane metalloproteinase which is responsible for the degradation of a variety of extracellular matrix (ECM). Many studies have shown that MT1-MMP plays a critical role in regulation of human leukocyte migration (Matias et al., 2005, Yang et al., 2006, Sithu et al., 2007). Sun et al reported connection between Bcr-Abl and MT1-MMP. They identified MT1-MMP as a novel downstream target of Bcr-Abl/Abi1 signaling pathways and also demonstrated that by activating the Abi1 pathway, Bcr-Abl induces a translocation of MT1-MMP to a membrane-associated structural complex enriched with F-actin and adhesion molecules. (Sun et al., 2008). Hence their result suggested that this membrane-associated structural complex may be used as good prognostic marker. The role of angiogenesis in the pathogenesis was evaluated in Bcr-abl positive cells in chronic myelogenous leukemia (CML) and assessed the effects of the bcr-abl translocation on the secretion of angiogenic factors VEGF, FGF-2, HGF, IL-8 and matrix metalloproteinases (MMPs) in vivo of bcr-abl positive cells. Finally, concluded that stimulation of angiogenesis by angiogenic factors, including MMPs, could play an important role in the pathogenesis of CML (Janowska et al., 2002).

As literature showed that gelatinases A and B is the major MMP produced by B-CLL cells and contributes to their tissue infiltration by degrading extracellular and membrane-anchored substrates. Redondo-Muñoz et al describe a different function for MMP-9 in B-CLL, which involves the hemopexin domain rather than its catalytic function and very interesting data concluded that MMP-9 promotes chronic lymphocytic leukemia B cell survival through its hemopexin domain (Redondo et al., 2010). Also identified that α4β1 and CD44v may used as a novel proMMP-9 cell surface docking complex and showed that cell-associated MMP-9 may regulate B-CLL cell migration (Redondo et al., 2008). Recently, Ugarte-Berzal et al reported that MMP9 hemopexin domain binds α4β1 integrin and inhibits MMP-9-induced functions in chronic lymphocytic leukemia B cells. Therefore, they constitute an excellent target to prevent proMMP-9 contribution to B-CLL pathogenesis (Ugarte et al., 2012).

Continuous secretion of MMP-9 can be observed in mature monocytes/macrophages and T-lymphocytes as well as malignant B-lymphocytes (Barille et al., 1997). Neutrophil granulocytes also synthesize MMP-9 in these cells because enzyme production in these cells starts at the stage of myelocyte/metamyelocyte differentiation. Therefore, MMPs secretion and transcriptional regulation participate in the activation or progression of disease in haematological malignancies. Reis et al first analyze MMP production in human ex vivo bone marrow cells and showed that BM-MNCs continuously produce MMP-9 and TIMP-1 and demonstrated that leukemic blast cells additionally secrete MMP-2 representing a potential marker for dissemination in myeloproliferative malignancies (Ries et al., 1999).

Updates of Matrix Metalloproteinase Inhibitors (MMPIs) in Clinical Use

Many studies have shown that several types of MMPs contribute in solid and soft tumors. MMPs promote cancer progression by increasing cancer-cell growth, migration, invasion, metastasis and angiogenesis. The balance between MMPs and TIMPs is critical for the proper maintenance of functional homeostasis in hematopoietic tissue and also in solid tumors. The role of matrix metalloproteinases (MMPs) in cancer angiogenesis, growth and metastasis provoked researchers to search for ways to inhibit these MMPs. This has resulted in the investigation of approximately 50 MMPIs which have undergone various phases of clinical trials. However, despite a large number of studies being carried for discovery and development of MMPIs, results have largely not been supportive of this approach to anticancer treatment. MMP participated into various functions. We mentioned most significant function of MMPs like activation of vascular endothelial growth factor (VGEF), migration of keratinocytes, adipocyte differentiation, regulation tumorigenesis etc in Figure no 2 (Figure 2).

Last 50 years, pharmaceutical industries have focused their work on developing novel drugs that can target development of different malignant cells. MMPIs are used in the treatment of cancers such as leukemias, lymphomas, testicular cancer, lung, gastrointestinal, oropharangial cancer. But unfortunately all the therapies had side defects. MMPIs may inhibit malignant growth by enhancing fibrosis around malignant lesions; by this they prevent tumor invasion, apoptosis and angiogenesis. Inhibitors of MMPs fall into five categories such as Peptidomimetics, Nonpeptidomimetics, Natural MMPIs, Tetracycline like

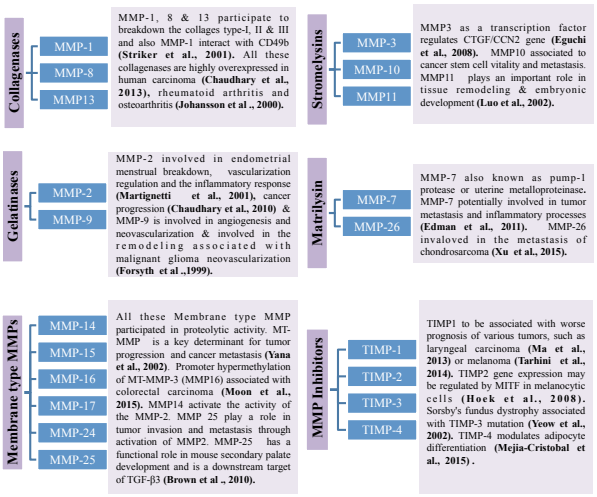

Figure 1. Classification and Functions of Human MMPs and Their Inhibitors

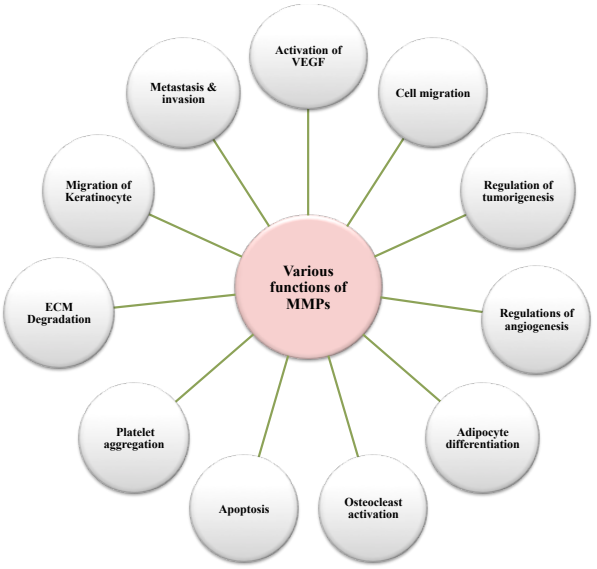

Figure 2. Various Biological Functions Facilitated by Matrix Metalloproteinases (MMPs) Cleavage in Tumorigenesis

derivatives and bisphosphonates. A naturally-occurring protein and a non-functional serine protease inhibitor and pigment epithelium-derived factor (PEDF), have been proposed for cancer therapy partly due to its ability to regulate specific MMPs central to cancer progression (Alcatara et al., 2014). The extrapolation of MMPs in the major stages of cancer progression has driven interest in the design of synthetic MMP inhibitors (MMPIs) used as a novel anticancer therapy (Maquoi et al., 2004).

It is thought that by inhibiting the MMPs, angiogenesis and metastasis can be inhibited. COL-3, (NSC-683551), a matrix Metalloproteinases inhibitors is used for the treatment of the refractory metastatic cancer. COL-3 is a chemically modified tetracycline that targets multiple aspects of matrix metalloproteinase regulation (Rudek et al., 2011). These drugs are currently in Phase I human trials. While, in advanced soft tissue sarcomas MMPI COL-3 are in phase II clinical trial (Chu et al., 2007). In reported clinical trials, COL-3 exerted the strongest anti-proliferative and pro-apoptotic effects. These results indicate that there is a therapeutic potential of Tetracycline analogues (TCNAs) in HL60 acute myeloid leukemia (Song et al., 2014). Parvathy et al reported that Matrix metalloproteinase inhibitor COL-3 prevents the development of paclitaxel-induced hyperalgesia in mice and suggested that it could be useful in the prevention of chemotherapy-induced painful neuropathy (Parvathy et al., 2013). MMPs are also involved in tumor metastasis and are overexpressed in Kaposi's sarcoma (KS) cells. MMP inhibitor COL-3 in patients with AIDS-related KS, Phase I drug was well tolerated, KS regression was observed, and MMP-2 levels decreased significantly in responders compared with non-responders. Dezube reported that COL-3, when administered as 50 mg/d, is both active and well tolerated in the treatment of KS cells and concluded that COL-3 is a promising agent for the treatment of the neoplasm of AIDS associated with KS cells (Dezube et al., 2006). Another study also suggested that matrix metalloproteinase inhibitor COL-3 could be used for the treatment of AIDS-related Kaposi's sarcoma (Cianforcca et al., 2002).

Over all we concluded that MMP inhibitors might be more effective for the treatment of different cancer. Many MMPIs have shown anti- leukemia activity in-vitro and in-vivo. So far, none of the inhibitors of the MMPs has been clinically tried in leukemic malignancies due to the inadequate knowledge of the exact roles of MMPs and its inhibitors. Therefore, future studies should first clarify the dysfunction of the MMPs production by different oncogenic subsets in pathogenesis of different malignancy and then identify specific MMP targets to improve anti-leukemia and anti- tumorigenic efficacy.

Conclusions

Till date biological behaviour of pleotropic role of the matrix metalloproteinase (MMPs) and its tissue inhibitors (TIMPs) are well known in many malignancies. The more number of *in vitro* and *in vivo* studies are required to know the exact biological roles of MMPs and TIMPs in malignancies in early and late stages. But unfortunately, the most of the studies carried out have not well set to find out the novel biomarkers to predict the early prognosis of the disease. The discovery of novel prognostic markers will promote new possibilities for the cancer treatment. The uses of broad-spectrum MMP inhibitors (MMPIs) for treating the patients with cancer are growing rapidly. However, their efficacy and action have not been confirmed and more data is required to accumulate an important therapeutics axis for management of cancer cure. The more number of studies and multi-institutional collaborations will help in the development of the better prognostic markers.

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