Chapter

Potential Roles of Matrix Metalloproteinases in Malignant Mesothelioma

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Abstract

Malignant mesothelioma (MM) is a rare, aggressive, and highly lethal cancer that is primary induced by exposure to asbestos fibers. Matrix metalloproteinases (MMPs) are a family of zinc-dependent endopeptidases that are involved in metastasis, and their overexpression correlates with tumor cell invasion and metastasis because they degrade the extracellular matrix (ECM) and process adhesion and cytoskeletal proteins, growth factors, chemokines, and cytokines. Recent evidence has shown that MMPs participate in MM progression, indicating that they are potential novel biomarkers and attractive targets for cancer therapy. In this chapter, we will describe MMPs in carcinogenic mechanisms based on in vivo and in vitro experimental evidence, outline the clinical findings, and speculate the possible roles of MMPs in MM.

Keywords: malignant mesothelioma, matrix metalloproteinases, mesothelial carcinogenesis, extracellular matrix, biomarker

1. Introduction

Malignant mesothelioma (MM) is a rare, aggressive cancer that originates from mesothelial tissue in the pleura, peritoneum, and pericardium; MM has been associated with asbestos exposure, especially in occupational settings [1]. In some countries, such as Turkey and Japan, MM is also due to environmental asbestos exposure, which affects people who live in the vicinity of natural asbestos mines or factories that use asbestos [2–4]. Mesothelioma is highly resistant to conventional cancer therapies. MM patients usually have a poor prognosis, with a median survival of 12–18 months, due to the lack of effective treatments and difficulty in diagnosing this disease at the early stage [5–7]. In general, there are three main histological subtypes of mesothelioma. The epithelioid and sarcomatoid subtypes are characterized by cuboid and fibroblastoid cells, respectively. The biphasic subtype contains a mixture of both cell types and confers the worst prognosis. The most widely used treatments for MM are surgery with or without adjuvant chemotherapy and/or radiotherapy [8]. The first-line treatment option for unresectable MM is chemotherapy with cisplatin plus pemetrexed [9, 10]. Nevertheless, MM may be resistant to these conventional therapeutic approaches, and palliative care strategies are controversial. Although crocidolite and/or chrysotile have not been used for more than 10 years in many developed and developing countries, high mortality

rates associated with mesothelioma persist since the clinical manifestations of MM are insidious and nonspecific. It is worth noting that MM has a long latency period (mean, 30–40 years) from the time of asbestos exposure to tumorigenesis [4, 11]. Thus, valuable biomarkers for the prediction or diagnosis of MM at early stages, prognostic markers, and novel therapeutic strategies are urgently needed.

Matrix metalloproteinases (MMPs, also known as matrixins) are a family of zinc-dependent endopeptidases that degrade all components of the extracellular matrix (ECM); thus, MMPs are involved in ECM remodeling. In addition to functioning as the main ECM regulators, MMPs also modulate intra- and extracellular signaling pathways and networks through the proteolytic processing of various biomolecules. The first MMP was reported by Gross and Lapiere as a collagenase engaged in tail resorption during tadpole metamorphosis [12]. To date, 24 MMP genes, including a gene duplication, that encode 23 unique MMP proteins have been identified in humans [13, 14]. According to substrate specificity, sequence similarity, and specific role, MMPs can be divided into eight main groups: (1) collagenases (MMP-1, MMP-8, and MMP-13), (2) matrilysins (MMP-7 and MMP-26), (3) metalloelastase (MMP-12), (4) stromelysins (MMP-3, MMP-10, and MMP-11), (5) gelatinases (MMP-2 and MMP-9); (6) enamelysin (MMP-20); (7) membrane-type MMPs (MMP-14, MMP-15, MMP-16, MMP-17, MMP-24, and MMP-25), and (8) others (MMP-19, MMP-21, MMP-23, MMP-27, and MMP-28) [13, 15]. Interestingly, the proteolytic activities of MMPs are precisely controlled by activation of their precursors and inhibition by endogenous inhibitors, α-macroglobulins, and tissue inhibitors of metalloproteinases [13]. Except for six membrane-associated MMPs, the other 17 MMPs are soluble secreted enzymes [16]. In addition, growth factors, chemokines, and cytokines modulate the expression of MMPs through various pathways to affect ECM degradation and, in turn, influence growth factors, which ultimately affect cancer cell migration and invasion [17, 18].

Of note, MMPs are expressed in various cancer tissues, and their expression levels are closely associated with the properties of invasive growth and metastasis [15]. Accumulating evidence suggests that ECM degradation by MMPs at the cell surface enhances tumor growth, invasion, and metastasis through the proteolytic degradation of ECM, altered cell-cell, and cell-ECM interactions and effects on cell migration and angiogenesis [17, 19]. More recently, the roles of different MMPs have become increasingly studied in the field of MM research. Experimental evidence indicates that MMP-1, MMP-2, and MMP-9 are involved in mesothelial carcinogenesis. Several MMPs, such as MMP-7, MMP-14, and MMP-9, are potential biomarkers for MM. In the following sections, we will describe the roles of MMPs in carcinogenic mechanisms based on in vivo and in vitro experimental evidence, outline the clinical findings, and highlight the possible roles of MMPs in MM, as well as future prospects.

2. Crucial roles of MMPs in mesothelial carcinogenesis

Some MMPs are upregulated and considered mesenchymal markers of epithelial-to-mesenchymal transition (EMT), such as MMP-1, MMP-2, and MMP-9 [20]. EMT not only is associated with many physiological processes, such as embryonic development, but also plays a vital role in pathological processes, including cancer cell invasion and migration [21–23]. During EMT, epithelial cells lose their phenotype and acquire a mesenchymal phenotype, including the loss of cell polarity and cell adhesion in cell-cell and cell-basement membrane interactions and the acquisition of ECM degradation ability, which is directly related to MMPs. Currently, published studies implicate MMPs as inducers of EMT during MM progression. In

addition, MMPs play a mediator role in cellular signaling pathways controlled by growth factors and cytokines [17, 24]. Here, we describe these two main roles of MMPs in MM carcinogenesis. Moreover, we propose possible mechanisms involving MMPs, as shown in **Figure 1**.

2.1 EMT inducer

MMP-1 is an interstitial collagenase that specifically targets the degradation of collagen types I–III [25]. Schelch et al. reported that in malignant pleural mesothelioma (MPM) cells in vitro, fibroblast growth factor 2(FGF2) and epidermal growth factor (EGF) may induce EMT via mitogen-activated protein kinase kinase (MEK)/MMP-1 signaling [26]. The experimental results indicated that MMP-1 inhibition by the pan-MMP inhibitor GM6001 or transfection with siRNAs targeting MMP-1 could prevent FGF2-induced cell scattering and invasion in the M38K cell line (a biphasic MPM cell line) [26]. In MPM tissue specimens, higher MMP-1 expression was observed in the sarcomatoid compartment than in the epithelioid compartment. Normal pleura were weakly positive for MMP-1 [26]. These results suggest that MMP-1 causally contributes to sarcomatoid morphology and increases cell invasiveness during EMT.

MMP-2, also named gelatinase A, is expressed by almost all cell types, and its classical substrates are denatured collagen (gelatin) and basement membrane [25, 27]. Indeed, MMP-2 acts as a cancer-associated EMT inducer or modulator in a number of tumors, such as breast cancer [16, 28], hepatocellular carcinoma [29], prostate cancer [30], ovarian cancer [31], oral squamous cell carcinoma [32], and MM [33]. Regarding MM, MMP-2 secretion from human normal mesothelial MeT-5A cells increased upon treatment with chrysotile or transforming growth factor-β (TGF-β) [33], and EMT was induced. This in vitro experimental result of increased MMP-2 secretion by cells exposed to chrysotile asbestos suggests changes in the surrounding microenvironment that render the ECM more amenable to degradation and invasion [33, 34]. Of course, the underlying mechanism of MMP-2-induced EMT in MM development requires further study.

MMP-9 is a type IV collagenase also known as gelatinase B [35] that has a similar ability to cleave gelatin as MMP-2. MMP-9 has been recognized as an EMT mediator in cancer progression and appears to be a potential therapeutic target [35–37].

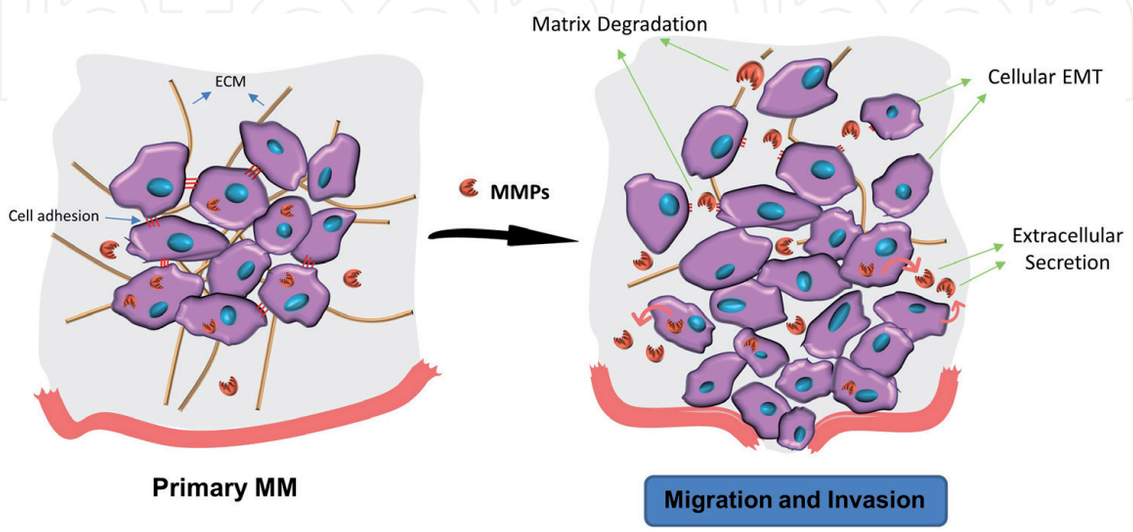

Figure 1.
Schematic representation of MMP-involved mechanisms in MM carcinogenesis. See detail in text. MM, malignant mesothelioma; EMT, epithelial-to-mesenchymal transition; ECM, extracellular matrix.

Elevated MMP-9 levels were observed in a 3D microtumor model of patient-derived mesothelioma cells, consistent with the elevated MMP-9 levels in patient breast tumors compared to healthy mammary glands [38]. Moreover, MMP-9 secreted into conditioned media by large microtumors induced a migratory phenotype in nonmigratory small microtumors, and blocking MMP-9 with GM6001 effectively abolished the collective migration of mesothelioma microtumors [38]. These findings imply that a self-regulated positive feedback loop involving MMP-9 is established during tumor progression and migration [38]. Additionally, the invasion of H2052 (mesothelioma cell line) and JP5 cells (primary mesothelioma cell line) into a 3D collagen matrix induced by gremlin-1 (a protein antagonist of bone morphogenetic proteins) was significantly alleviated by GM6001 and BB2516 (broad-spectrum MMP inhibitors) [39]. Interestingly, in our previous study, we found that serum MMP-2 and MMP-9 levels were correlated with each other in both healthy control and MM groups in a Han cohort from Eastern China [40]. Nevertheless, there were no significant differences in MMP-2/MMP-9 levels between the healthy control and MM groups.

2.2 Signaling pathway mediator

Various growth factors, cytokines, and miRNAs engage specific cellular signaling pathways, such as the MEK and extracellular signal-regulated kinase (ERK) signaling pathways, to regulate MMP expression levels to degrade the ECM, and MMPs then contribute to the release of tumor-related factors, such as vascular endothelial growth factor and TGF-β, from the ECM [17, 24].

MMP-1 expression showed an increasing trend in MM cell lines from no treatment to treatment with FGF2 and EGF and a pronounced decrease upon treatment with selumetinib (MEK inhibitor), suggesting that the growth factors FGF2 and EGF regulate MMP-1 expression via the MEK signaling pathway in MM [26]. TGF-β, another important growth factor that regulates cell growth and differentiation, affects MMP-2 expression in MeT-5A [33] and JL-1 cells [39]. Moreover, growth hormone-releasing hormone (GHRH) antagonists (MIA-602 and MIA-690) equally blunted MMP-2 and MMP-9 mRNA levels in both REN and MSTO-211H cells (MM cell lines), indirectly indicating that MMP-2/MMP-9 expression is induced by GHRH [41], as well as by adenosine diphosphate in ZL55 cells (an epithelioid MM cell line), via the nuclear factor kappa-B, protein kinase B, and ERK1/2 signaling pathways [42]. Interestingly, microtumor treated with GM6001 showed reduced pERK/ERK ratios and ERK activation [38]. Notably, miR-591 targets MMP-2 expression, and overexpression of miR-591 inhibited MMP-2 levels in MPM cells [43]. These experimental results show that MMP expression is regulated by various factors via multiple signaling pathways and that MMPs interact with such inducers and signaling pathways in MM carcinogenesis.

3. Potential roles of MMPs as biomarkers for MM

3.1 Pathological markers

To date, MM is still difficult to diagnose in early stages due to our limited knowledge of its molecular pathogenesis. Indeed, pathological examination techniques to diagnose MM and distinguish MM from other diseases must be improved [44]. However, more molecular markers are required to distinguish benign from malignant mesothelial disease or other tumors. In addition, effective pathologic predictors of prognosis and therapeutic response are urgently needed. Since MMPs are involved in tumor pathogenesis, some MMPs may be potential pathological markers.

In general, MMP expression and activation are very low and tightly regulated during normal tissue homeostasis. MMP production and activation are rapidly induced during active tissue remodeling and in pathological conditions such as cancer [37]. MMP-7 and MMP-14 are potential diagnostic and prognostic biomarkers of mesothelioma, respectively. MMP-7 is a highly specific negative biomarker to distinguish MM from other high-grade serous carcinomas with 100% specificity and moderate sensitivity, but it cannot distinguish mesothelial cells from reactive mesothelial cells in serous effusion due to uniformly negative expression of MMP-7 in reactive mesothelial cells [45]. It is intriguing that MMP-14 is a potential biomarker for the differential diagnosis of MPM and reactive mesothelial hyperplasia (MH). A group from Italy found that MMP-14 expression is markedly increased in MPM patient specimens compared with MH specimens based on polymerase chain reaction array and immunohistochemistry analyses [46]. MMP-14 levels have been reported to be elevated in all tissue samples from MM patients compared to those from normal individuals, but more evidence is needed to substantiate MMP-14 as a diagnostic biomarker for MM [47]. MMP-14 expression has prognostic value for MM. Clinically high MMP-14 expression in MM patients is significantly correlated with poor prognosis [47].

3.2 Genetic biomarkers

Although most mesotheliomas are attributable to asbestos exposure, genetic factors are also important causes of carcinogenesis. Gene mutations influence the prognosis of MM. For example, heritable mutations in BRCA1-associated protein-1 (BAP1), a tumor suppressor gene, may predispose individuals to asbestos-related MM [48, 49]. Moreover, Baumann et al. reported that mesothelioma patients with germline BAP1 mutations have a seven-fold improvement in long-term survival [50].

More recently, some MMP single-nucleotide polymorphisms (SNPs) have been found to have potential as genetic biomarkers for MM. For instance, Štrbac et al. reported that patients carrying a polymorphic MMP-9 rs2250889 allele had a negative outcome, with a shorter time to progression (TTP) (6.07 vs. 10.03 months, HR = 2.45, 95% CI = 1.45–4.14, p = 0.001) and worse overall survival (OS) (9.23 vs. 19.2 months, HR = 2.39, 95% CI = 1.37–4.18, p = 0.002) than those with the reference allele [51]. However, patients harboring at least one polymorphic MMP-9 rs20544 allele had a positive outcome, with a longer TTP (10.93 vs. 9.40 months, HR = 0.57, 95% CI = 0.38–0.86, p = 0.007) and improved OS (20.67 vs. 13.50 months, HR = 0.56, 95% CI = 0.37–0.85, p = 0.007) [51]. These researchers also found that the MMP-2 rs243865 polymorphism plays a protective role in MM; carriers of this polymorphism have a decreased risk for MM (OR = 0.66, 95% CI = 0.44–1.00, p = 0.050) [52]. Interestingly, the decreased risk for MM is more pronounced in people exposed to asbestos [52]. These findings provide insight into some MMP SNPs that are considered genetic biomarkers, indicate the prognosis of MM patients, and predict susceptibility to MM. In the future, appropriate genetic counseling and clinical management should be considered for MM patients who are carriers of MMP-2/MMP-9 susceptibility SNPs.

4. Conclusion

In this chapter, we provide an overview of recent findings on MMP function in MM and the mechanisms by which MMPs may induce both phenotypic and genotypic alterations that facilitate MM progression and invasion. Accumulating evidence indicates that tumor-associated MMPs can stimulate processes associated

with EMT, a developmental event that is activated in MM cells during invasion and metastasis. Meanwhile, future investigations on extracellular targets and intracellular signaling pathways through which MMPs can induce EMT of MM cells will provide insight into novel therapeutic targets. We also describe possible roles of MMPs as pathological markers or genetic biomarkers in MM. Certainly, the underlying mechanisms of secreted MMPs, including their function and circulation, are complex in MM and remain to be elucidated in the future.

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Conflict of interest

The authors declare no conflicts of interest.

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