Multifunctional matrix metalloproteinases; targets for cancer treatment (Review)

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Introduction: Cancer is the most important death cause in both industrial and developing countries, and metastasis is the major cause of cancer morbidity and mortality. Matrix metalloproteinases (MMPs) or matrixins are a family of calcium- and zinc-dependent endopeptidases with extra and intracellular functions. Based on domain organization, sequence similarity and substrate specificity, MMPs are classified as collagenases, gelatinases, stromelysins, matrilysins, transmembrane type I, transmembrane type II and glycosylphosphatidylinositol-anchored MMPs. MMPs orchestrate metastatic events including modulation of tumor microenvironment (by disruption of basement membrane and extracellular matrix molecules), secretion and activation of chemokines, cytokines, growth factors, adhesion molecules and cytoskeletal proteins, production of angiogenic factors, recruitment of myeloid populations and inhibition of immune surveillance. The present review considers current therapeutic strategies that inhibit MMPs.

Methods: Recent reports included key words matrix metalloproteinases, target therapy, cancer metastasis were extracted from databases PubMed, Web of Science and Scopus.

Results: As understanding of MMPs' function in cancer metastasis has greatly improved in recent years, safe and effective agents have been developed to regulate the expression and activity of these enzymes. Current strategies target MMPs at transcription level (via transcription factors like HIF-1 and NF-κB or and signaling pathways such as MAPK and ERK), translation level (by antisense strategies), inactivation of pro-MMPs (using monoclonal antibodies) and blocking the proteolytic activity by MMP inhibitors (MMPIs). MMPIs are divided as the following; Peptidomimetics that are pseudopeptide derivates simulating the structure of a peptide sequence identified by MMPs (drugs like Batimastat and Marimastat); Non-peptidomimetics that are designed according to the 3D X-ray crystallography structures of MMPs' active site (drugs such as Prinomastat, Rebimastat and Tanomastat); Chemically modified tetracyclines with no antibiotic activity (drugs like Doxycycline and Minocycline) and Off target inhibitors that diminish MMPs enzymatic activity (such as Zoledronic acid and Letrozole).

Conclusion: Therapies designed to interfere with expression and activation of MMPs may be useful in the control of metastatic disease, and thus, improve the overall survival of cancer patients.

Keywords: Matrix metalloproteinases, Target therapy, Cancer metastasis.