MT1-MMP in Cancer Progression

Subjects: Others

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For over 20 years, membrane type 1 matrix metalloproteinase (MT1-MMP) has been recognized as a key component in cancer progression. Initially, the primary roles assigned to MT1-MMP were the activation of proMMP-2 and degradation of fibrillar collagen. Proteomics has revealed a great array of MT1-MMP substrates, and MT1-MMP selective inhibitors have allowed for a more complete mapping of MT1-MMP biological functions. MT1-MMP has extensive sheddase activities, is both a positive and negative regulator of angiogenesis, can act intracellularly and as a transcription factor, and modulates immune responses. We presently examine the multi-faceted role of MT1-MMP in cancer, with a consideration of how the diversity of MT1-MMP behaviors impacts the application of MT1-MMP inhibitors.

Keywords: matrix metalloproteinase ; extracellular matrix ; cancer progression ; immunosuppression ; signal transduction ; collagenolysis

1. Introduction

Membrane type 1 matrix metalloproteinase (MT1-MMP) was initially identified as a cell surface protease present in tumor cells. Since then, MT1-MMP has become a highly sought after target in cancer therapy. The expression of MT1-MMP has been associated with poor prognosis in patients with melanoma, pancreatic cancer, advanced neuroblastoma, small cell and non-small cell lung cancer, mesothelioma, tongue squamous cell carcinoma, head and neck carcinoma, bladder cancer, breast cancer, colorectal cancer, and ovarian cancer. Increased tumor cell expression of MT1-MMP enhances metastasis. MT1-MMP induces the epithelial to mesenchymal transition (EMT) in prostate and squamous cell carcinoma cells. MT1-MMP is needed for tumor cell transmigration through endothelium and basement membrane invasion. Gliomas induce MT1-MMP expression and activity in microglial cells. Cancer stems cells/tumor-initiating cells require MT1-MMP for growth, tumor initiation, invasion and metastasis, particularly in hypoxic, nutrient-deprived environments. MT1-MMP is generally considered pro-invasive and pro-tumorigenic as (a) the expression and activity of MT1-MMP are elevated in tumor tissues and (b) high levels of MT1-MMP directly correlate with enhanced cell migration and tumor regional invasion/remote metastasis.

While extensive data indicates a significant role for MT1-MMP in cancer, studies of MT1-MMP have often focused on its activation of proMMP-2, hydrolysis of collagen, and shedding of CD44. Mass spectrometric analysis of biotin-labeled cell surface proteins revealed 158 binding partners for MT1-MMP. MT1-MMP cell surface binding partners that have been validated include tetraspanins (CD9, CD37, CD53, CD63, CD81, CD82, CD151, and/or TSPAN12), the α2β1 and αvβ3 integrins, CD44, and a ternary complex with tetraspanins and the α3β1 integrin. Proteomic approaches have uncovered a vast array of potential MT1-MMP substrates . Advancements in bioanalytical methods have revealed that the precise behaviors of MT1-MMP that contribute to disease initiation and progression are now greater than believed even a few years ago.

2. functions and development

The initial view of the role of MT1-MMP in cancer progression was straightforward: activation of proMMP-2 and degradation of fibrillar collagen to facilitate metastasis. The contributions of MT1-MMP to cancer progression are now viewed as far more complex based on the number of MT1-MMP substrates identified. MT1-MMP activity has a negative impact on immune responses to tumors, and intracellular MT1-MMP activity regulates cancer cell metabolic functions. MT1-MMP has a significant role in angiogenesis, whereby it can exhibit both pro-angiogenic and anti-angiogenic behaviors. These contrasting behaviors point to the importance of the spatial and temporal expression of MT1-MMP. Active MT1-MMP has been found to be highly expressed in stromal cells of the tumor microenvironment (cancer-associated fibroblasts, macrophages, etc.) rather than the tumor epithelium in mouse models of pancreatic and breast cancer. Thus, there are considerations as to how the tumor induces MT1-MMP production. The tumor microenvironment also impacts MT1-MMP activity based on the local pH and oxygen and nutrient content.

Several creative strategies have led to the development of highly selective MT1-MMP activity inhibitors. Of particular interest would be approaches that avoid active site targeting of MT1-MMP, in consideration of prior failures of active site targeting MMP inhibitors in clinical trials. Numerous antibodies have been described that modulate MT1-MMP proteolytic activity by interacting with secondary binding sites (exosites). In a similar fashion, the compound NSC405020 [3,4-dichloro-N-(1-methylbutyl)benzamide] was found to bind to the MT1-MMP HPX domain, inhibit MT1-MMP homodimerization, and reduce tumor size significantly in mouse models. Inhibitors could be designed to disrupt cell surface complexes, such as MT1-MMP association with tetraspanins, the α2β1 and αvβ3 integrins, CD44, and the ternary complex with tetraspanins and the α3β1 integrin. Peptide IS4 (acetyl-VMDGYPMP-NH2), modeled on the region of the MT1-MMP HPX domain that binds CD44 (the outermost strand of blade I), inhibited MT1-MMP-mediated cell migration and metastasis in vivo. CT interactions of MT1-MMP can be inhibited using a peptide model (7R)-CPT (RRRRRRRGRRHGTPRRLLYCQRSLLDKV), resulting in decreased tumor growth. Inhibitors of signaling pathways that impact MT1-MMP function can also be utilized to modulate the enzyme. In order to impact cancer in a positive way, the successful application of these inhibitors will require a thorough consideration of mode of administration (systemic versus topical), mechanism of action (extracellular versus intracellular), cancer stage (pre-metastatic versus metastatic), and potential side effects. It is worth noting that the inhibition of MT1-MMP activity in triple-negative breast cancer mouse models improved tumor profusion and sensitized the tumor to ionizing radiation or doxorubicin treatments.
