Chapter 6

MEMBRANE-TYPE MATRIX METALLOPROTEINASES

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1. INTRODUCTION

Matrix metalloproteinases (MMPs) can be divided into two groups; the membrane bound or membrane-type MMPs (MT-MMPs), and the soluble MMPs (Seiki, 1999; Nagase and Woessner, 1999). MT-MMPs have a membrane-anchoring sequence at the carboxyl terminus leading to the expectation that they would degrade extracellular matrix (ECM) at the periphery of cells whereas soluble MMPs might be capable of degrading ECM distant from the producer cells in the tissue. Tissues are comprised of cells embedded in a framework of ECM in which the cells and the ECM are attached through cell surface adhesion molecules. The cells in tissue may need to modify the pericellular ECM environment for cellular functions, such as proliferation, migration or the alteration of cell morphology. An association of MMPs with the cell surface may facilitate the ECM remodeling associated with such cell functions (Werb, 1997; Murphy and Gavrilovic, 1999).

Malignant cancer cells are characterized by their ability to invade into surrounding tissue and finally metastasize to distant organ. MMPs are the major players for the ECM degradation associated with cancer cell invasion (Stetler-Stevenson et al, 1993; McCawley and Matrisian, 2000). Many MMPs are expressed at high levels in cancer tissues and they collectively contribute to the proliferation of the tumor cells and invasion into surrounding tissue. Particularly, MMPs associated with the cancer cell surface are expected to play important roles during such processes. In this review, we summarize recent information about MT1-MMP and other MT-MMPs.
2. STRUCTURE OF MT-MMPS

Among the over 25 mammalian MMPs, six are MT-MMPS having an anchoring device to the plasma membrane at the C-terminus (Figure 1). All the six MT-MMPS have common structural characteristics. Adjacent to the cysteine switch in the propeptide, MT-MMPS have a multi-basic amino acid motif containing a recognition site for proprotein convertases such as furin and its related proteinases (Hosaka et al, 1991). Some soluble MMPs, MMP-11 (stromelysin 3), and MMP-23 also have this motif (Nagase and Woessner, 1999). The presence of this motif leads to the expectation that proMT-MMPS will be activated intracellularly and delivered to the cell surface as an active enzyme. MT-MMPS have catalytic and hemopexin-like domains in common with the soluble MMPs.

Figure 1. Domain structure of MT-MMP. MT-MMPS are unique among MMP family members in that they have a plasma membrane anchoring device at the carboxyl terminus. They also have a multi-basic motif at the cleavage site for the processing of propeptide by subtilisin family proteinases. The multi-basic motif is also present in MMP-11, and MMP-23. The C-terminal hydrophobic stretch of proMT4-MMP and proMT6-MMP are cleaved off during secretion and transferred to glycosylphosphatidyl inositol (GPI) anchor. Pro: propeptide; Catalytic: catalytic domain; Hemopexin: Hemopexin-like domain; GPI: glycosylphosphatidyl inositol; TM/CP: transmembrane and convertase processing.