Chapter 10

CLINICAL ASPECTS OF MATRIX METALLOPROTEINASES

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Abstract
Tumor metastasis is ultimately responsible for most cancer deaths. Tumor invasion and metastasis represent a multistep process including basement membrane disruption, stromal infiltration, angiogenesis, intravasation and extravasation and invasion of target organs by tumor cells. All these events require degradation and remodeling of the extracellular matrix (ECM) by various proteolytic enzymes. Among these enzymes, matrix metalloproteinases (MMPs) play a key role at various levels. These enzymes are associated with degradation of a broad spectrum of ECM components. MMPs are also implicated in the remodeling the ECM by creating and maintaining a microenvironment that facilitates angiogenesis and growth of tumors. Thus, in the last years, the exploration of MMPs expression has led to a large bunch of studies on their biological activities and their clinical implications.

1. THE MMP FAMILY

The MMP family consists of 4 principal subclasses which include the collagenases, the gelatinases (type IV collagenases), the stromelysins, and the Membrane-Type MMPs (MT-MMPs) (Nagase and Woessner, 1999). These enzymes are secreted and are membrane-bound in a latent, proenzyme form and require activation to digest ECM components. The activation process consists in a proteolytic cleavage of a propeptide domain at the N-terminus of the MMP molecule which can be accomplished by proteolytic enzymes including plasmin and other MMPs. For example, most of the MT-MMPs participate in the activation of pro-MMP-2. After this activation, most MMPs are able to degrade a broad spectrum of ECM components, allowing tumor cells to penetrate the stroma. The interstitial collagenases (MMP-1, MMP-8, MMP 13 and MMP-18) cleave a specific peptide bond in triple helical fibrillar collagens I, II and III. The two gelatinases A (MMP-2) and B (MMP-9) target denatured collagen, gelatin and the type IV collagen present in basement membranes. The stromelysins have the broadest spectrum of substrates, cleaving proteoglycans, gelatin, laminin, fibronectin. This subfamily includes stromelysin 1 (MMP-3),
stromelysin 2 (MMP-10), stromelysin 3 (MMP-11) and matrilysin (MMP-7). The last group encompasses five membrane-bound MMPs (MT1 to MT5-MMPs). There is a good evidence that one of their principal functions is to localize and activate secreted MMPs, particularly MMP-2 and MMP-13. However the role of MMPs is not limited to the ECM degradation. Indeed, recent studies implicate these enzymes in the activation of growth factors and/or their receptors, in the degradation of enzyme inhibitors, in the degradation of cell-matrix attachments, cell adhesion complexes and in the production of ECM products of degradation promoting angiogenesis and tumor invasion (Mc Cawley and Matrisian, 2000). Of particular interest is the case of MMP-11 (stromelysin-3). At the present time, no known ECM component has been reported degraded by this enzyme. Nevertheless it has been shown that this MMP-11 functions in vivo as a protease by remodeling ECM and probably by inducing it to release the necessary microenvironmental factors for tumor growth (Noël et al, 2000). This represents a new important role of MMPs and a new approach for understanding cancer progression.

MMP activity is regulated at multiple levels. At the transcriptional level, most of the MMP genes are responsive to a wide variety of growth factors, cytokines, hormones and oncogenes. Tissue inhibitors of MMPs (TIMPs) block enzymatic activity. At the present time, four members of the TIMP family are known, capable of binding and inhibiting the activity of all the members of the MMP family. However, TIMPs display differences in tissue distribution and differ in their capacity to form complexes with the inactive form of MMP and thereby in their ability to control MMP activation and activity. Interestingly, TIMP-2 is also involved in the activation process of MMP-2 as it binds to MT1-MMP and pro-MMP-2 at cell surface, resulting in proteolytic activation of the pro-MMP-2 by adjacent activated MT1-MMP (Strongin et al, 1995). TIMP-1 and TIMP-2 also display some growth factors properties (Bertaux et al, 1991; Stetler- Stevenson et al, 1992). Thus the regulation of MMPs activity cannot be reduced to a simple balance between MMPs and inhibitors.

2. DETECTION OF MMPs IN TUMORS

In the literature, various methodologies have been used for the detection of MMP expression in tumors. Numerous in vivo studies have reported the localization and production of these enzymes within tumor and stromal cells using immunohistochemistry and in situ hybridization. The expression of steady state level of mRNAs encoding MMPs in tumor tissues has been tested and quantified by Northern Blot and/or RT-PCR. In another way, zymographic detection for MMPs and reverse zymographic detection of TIMPs, western blot analyses