# 10. MATRIX METALLOPROTEINASES IN THYROID CANCER

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## INTRODUCTION

Cancer is a multistage disorder in which sequential and cumulative genetic aberrations lead to malignant cell transformation (1–2). Approximately 50% of cancer mortality results from invasion and metastasis. Tumor cell invasion and metastasis is a complex multistep process that involves the degradation of extracellular matrix (ECM) proteins by matrix metalloproteinases (MMPs), an important step in the process of cancer invasion and metastasis. Correlation between MMPs overexpression and cancer metastasis have been repeatedly made by numerous studies. Malignant cells rely on these proteinases to disrupt basement membranes, invade surrounding tissues and metastasize to different organs. It is now apparent that not only tumor cells but also non-malignant stromal cells actively participate in the proteolytic degradation of ECM. Tissue inhibitors of metalloproteinases (TIMPs) act as negative regulators of MMPs and it has been shown that they can prevent the spread of cancer in animal models by preserving ECM integrity (3–4).

Matrix metalloproteinases, also called matrixins, constitute a family of zinc–dependent endopeptidases. Twenty-eight members of this family have been identified. Collectively, MMPs play important roles in ECM homeostasis, mediating such normal physiological processes as embryogenesis, organ morphogenesis, reproduction, angiogenesis, and tissue resorption and remodeling (5). The proteolytic activities of MMPs are tightly regulated by endogenous inhibitors, $\alpha$-macroglobulins, and tissue inhibitors of metalloproteinases (TIMPs) (5). Any disruption of this fine balance can contribute

to the pathogenesis of serious diseases such as arthritis, periodontal disease, and cancer metastasis (6).

## THE MMP FAMILY AND STRUCTURE

At present, the human MMP family consists of 23 structurally related members (Table 1). Historically, the MMPs were divided into subgroups of collagenases, gelatinases, stromelysins, membrane-type MMPs, and other novel MMPs, on the basis of their specificity for ECM components. As the list of MMP substrates has grown and several MMPs can degrade a number of different ECM components, a sequential MMP numbering system has been adapted, and the MMPs are now grouped according to their structure. There are eight distinct structural classes of MMPs: five are secreted and three are membrane-type MMPs (Figure 1) (7).

MMPs are produced and secreted by a number of cell types, including fibroblasts, smooth muscle cells, and endothelial cells. They share several highly conserved domains, including an N-terminal propeptide domain that contains a "cystein switch" sequence that enfolds the zinc atom of the catalytic site to maintain the latency of pro-MMPs, a catalytic domain with a zinc binding site and a conserved methionine, and a C-terminal hemopexin-like domain linked to the catalytic domain by a proline rich hinge region. The catalytic domain contains a zinc binding motif HEXXHXXGXXH, in which the three histidine residues represent the three zinc ligands and the glutamic residue the active site. The hemopexin domain contains a single Cys-Cys bond and plays a role in substrate recognition (for example, it is required for collagenases to cleave triple helical interstitial collagens), interaction with TIMPs, and binding of the enzyme to ECM or cell surface (4–5).

The substrates of MMPs are primarily insoluble proteins of ECM, including interstitial and basement membrane collagens, glycoproteins such as laminin, fibronectin, vitronectin, tenascin and elastin as well as proteoglycans. However, more recent data demonstrate that certain MMPs can degrade proteins other than ECM proteins. Many cell membrane bound precursors of growth factors (TGF-$\alpha$, TGF-$\beta$), growth factor receptors (FGF receptor 1, HER2/neu, HER4) and cell adhesion molecules (CD 44, E-cadherin, $\alpha$v integrin) have been reported to be MMP substrates. For example, MMP-11 can cleavage of insulin-like growth-factor-binding protein (IGF-BP) to release IGFs (8); MMP-12 can proteolytically process plasminogen to generate angiostatin, an inhibitor of angiogenesis (9); MMP-2 and MMP-9 can proteolytically activate TGF-$\beta$ and promote tumor invasion and angiogenesis (10); and finally, cleavage of the $\alpha$v integrin subunit precursor by MMP-14 enhances cancer cell migration (11). Although the significance of these observations is not entirely clear, they reflect the complex nature of MMPs in cancer progression.

## REGULATION OF MMP ACTIVITY

The activities of MMPs are regulated at three major levels: transcriptional regulation, activation of latent MMP, and inhibition/deactivation by endogenous inhibitors such as $\alpha$-macroglobulins and TIMPs.