Remodeling of the extracellular matrix is a well-ordered biological process necessary for many functions, including tissue growth and regeneration, angiogenesis, collagen turnover, and cellular migration. Perturbation of the remodeling process is a hallmark of several diseases and pathological stages, such as tumor growth, invasion and metastasis, rheumatoid- and osteoarthritis, and a variety of pathologies that include neovascularization. Although several pathways for the degradation of extracellular matrices have been identified, the most universal yet-discovered utilizes enzymes known as matrix metalloproteinases (MMPs). MMPs are a family of highly homologous, zinc- and calcium-dependent endopeptidases that cleave most, if not all, components of the extracellular matrix.

More than 20 members of the family of human MMPs have been identified. The enzymes share a high degree of structural homology, but differ significantly in substrate specificity. Collagenases 1, 2, and 3 (MMPs 1, 8, and 13 or fibroblast, neutrophil, and osteoblast collagenases, respectively) efficiently degrade triple helical collagens I, II, and III at neutral pH. Gelatinases A and B (MMPs 2 and 9) degrade basement membrane collagen type IV, gelatin, and other proteoglycan components of the extracellular matrix. Highly related stromelysins 1 and 2 (MMPs 3 and 10) and the smallest member of the family, matrilysin (MMP 7), degrade various collagens, as well as fibronectin, laminin, and other proteoglycan components. In addition, the activity of various MMPs is required for activation of particular proteolytic cascades or for degradation of serpins, natural inhibitors of serine proteases.

Matrix metalloproteinases are expressed by many cell types in response to cytokines and growth factors, and in most cases are secreted as proenzymes. Enzyme activation in the extracellular environment requires coordinated activity of various serine proteases and an autoactivation step critical for optimal activity on natural substrates. In addition, the activation and activity of MMPs are further controlled by coordinated expressions of natural MMP inhibitors, the “tissue inhibitors of metalloproteinases” (TIMPs). In a variety of pathological processes, the balance of TIMP and MMP expression is perturbed, leading to locally increased proteolytic activity of MMPs and uncontrolled degradation of the extracellular matrix.
Expression of MMPs by tumors and surrounding stromal components has been studied extensively by in situ hybridization techniques, immunofluorescence, and enzyme zymography. The emerging pattern of MMP expression is complicated, and there is some controversy over which MMPs are most commonly associated with growing and invasive tumors.

*Matrix Metalloproteinase Inhibitors in Cancer Therapy* covers the entire field, from the biology of MMPs through current clinical studies. In the first half of the book several authors discuss the molecular mechanisms of the enzymes, substrates, and natural inhibitors, as well as the design strategy for MMP inhibitors. The remainder of the book is devoted to many of the individual pharmaceutical companies and their particular research on MMP inhibitors. Each company will approach this by discussing their own design strategy, providing the in vitro activity, animal model work, and if available, toxicology and human clinical trial safety and efficacy of their respective MMP inhibitors.

All of this represents a work in progress. We each recognize that our knowledge within this field is being expanded rapidly through new discoveries and analysis of current information. It is hoped that *Matrix Metalloproteinase Inhibitors in Cancer Therapy* not only provides a background for students, scientists, and clinicians, but will also help continue our efforts aimed at our understanding of the biologic process of extracellular matrix remodeling and its implications for human disease.

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