Preface to the Volume

The extracellular matrix is complex in its composition, wide ranging in its deposition, and diverse in how it shapes cell behavior and tissue organization. Critical to matrix function is the balance between deposition and turnover of its many, varied protein components. Indeed, the spatially and temporally precise removal and remodeling of connective tissue is critical to several developmental, homeostatic, and reparative processes. However, if matrix turnover and degradation are excessive and unregulated, as occur in many inflammatory conditions, bad things can happen. Because of the marked chemical diversity of matrix proteins – inclusive of glycoproteins, proteoglycans, and insoluble hydrophobic polymers, among other components – it is not surprising that the endopeptidases implicated in matrix turnover are equally diverse, both in their makeup and function. For example, the large and physiologically important serine proteinase family, which includes leukocyte elastase, plasminogen, and its activators, among many others enzymes, mediates a variety of activities, from clot dissolution to tissue destruction. Matrix metalloproteinases (MMPs), which compose a large subfamily within the even larger metalloproteinase family, have a specialized function in turnover of some extracellular matrix proteins, but as is discussed in more than one chapter in this volume, these enzymes are also effectors in other functions, particularly repair and immunity.

Essentially, all proteins transition through inactive, active, and finally deactivated states, and various posttranslational modifications mediate these changes. Proteolysis is one of several posttranslational mechanisms that regulate protein activity, and it is the principal way for ending a protein's time and recycling its amino acids for reuse. Evolution has provided us with six families of proteinases, defined by the amino acid or cofactor that catalyzes the nucleophilic attack on the peptide backbone of substrate proteins. Proteinases are found and operate both inside and outside of the cell. Many members of the cysteine, serine, and metalloprotienase families function extracellularly, and thus members of these three families have been implicated or demonstrated to function in turnover and degradation of the matrix. Hence, this volume focuses on these groups of enzymes.

Over the years, matrix metalloproteinases (MMPs) have gained considerable attention due to their suspected causative role in many destructive conditions, and this association has led to the oft-held idea that MMPs are the principal mediate of matrix turnover and degradation. However, in Chap. 1, Sean Gill and William Parks discuss that this assumption may not be as accurate as assumed and propose that MMPs and inhibitors have many diverse functions. If MMPs are not degrading as much matrix as we think, then who is? In Chap. 2, Dieter Brömme and Susan Wilson make a case for cysteine proteinases as major effectors of matrix remolding. Indeed, cysteine proteinases not only have been long known to degrade matrix (think osteoclasts), but they also make up much of the proteolytic machinery of lysosomes. Related this in both Chaps. 3 (Thomas Bugge and Niels Behrendt) and 8 (Vincent Everts and Paul Saftig), the authors discuss the important role of internalization to lysosomes in turnover of matrix, a process that has been too neglected in this field. In Chap. 4, Judith S. Bond, Timothy R. Keiffer, and Qi Sun discuss the membrane-bound serine proteinases and the essential roles these interesting enzymes serve in processing matrix and other extracellular proteins.

The next two chapters focus on structural mechanisms of how proteinases – with an emphasis on MMPs – interact with matrix substrates. In Chap. 5, Hideaki Nagase and Robert Visse discuss their interesting work on how MMP-1 can loosen a collagen triple helix making it more accessible to fit within the catalytic pocket of a metalloproteinases. In Chap. 6, Steven Van Doren presents sophisticated structural data on how the noncatalytic exosite regions of MMPs direct their interaction with matrix substrates.

The remaining chapters address on the role of matrix degradation in disease processes. In Chap. 7, James Quigley and Elena Deryugina discuss how MMPs promote multiple stages of tumor progression, from early transformation to metastasis, by acting on a variety of cell surfaces and matrix proteins to mediate different responses. As mentioned, in Chap. 8 Vincent Everts and Paul Saftig emphasize internalization as a critical component of matrix breakdown and turnover and so in the context of bone homeostasis and disease. In Chap. 9, A. McGarry Houghton, Majd Mouded, and Steven D. Shapiro focus on what is causing the breakdown of elastin, which occurs in devastating conditions such as emphysema and aneurysm formation.

We thank all authors for their effort and time and for their thoughtful and interesting contributions. We hope this volume on *Degradation of the Extracellular Matrix in Health and Disease* is of value for the many investigators and students with an interest in matrix biology, proteinases, and related topics.

Seattle, WA, USA — William C. Parks
St. Louis, MO, USA — Robert P. Mecham