Preface

About twelve years ago a colleague of mine lamented in a seminar that his studies of the mechanisms of action of a very famous growth factor had led him into the territory of heparan sulfate proteoglycans, which in his mind were second only to collagen in terms of boringness. Although he was certainly not alone in his opinion, which very likely extended to cover extracellular matrix molecules in general, those of us who study these proteins like to think that we have proven well beyond any reasonable doubt that a structural protein located outside of a cell can have a profound influence over cell behavior and tissue development and function. There exists a plethora of examples that demonstrate this, from simple multicellular organisms such as sponges, to our own complex species. Indeed, perhaps the most convincing argument that extracellular matrix proteins are worthy of our attention is that there are serious, relatively common human diseases that are caused by mutations in genes that encode these proteins. This has spurred a great number of researchers to study the extracellular matrix, sometimes by choice and sometimes by necessity, and much progress has been made in the last decade toward understanding what matrix proteins do and how cells interact with and respond to them.

This book is a compilation of reviews by leaders in the fields of extracellular matrix and cell/matrix interactions. Because it is beyond the scope of a book such as this to present a full picture of the extracellular matrix, I have designed it to focus on a diverse subset of matrix proteins that have been shown to be important for development, function, and disease. The book therefore both presents a broad view of the field and provides crucial details about some of the best-studied matrix molecules.

One of the most abundant proteins in the body is collagen, of which there are twenty-seven different types assembled from forty-two genetically distinct chains. The chapter by Harvey and Thorner focuses on type IV collagen, which is found ubiquitously and almost exclusively in basement membranes. Collagen IV has been found in all multicellular animal species, and for many years it was thought to serve as a requisite scaffold for basement membrane formation. However, recent data from mutant mouse embryos lacking collagen IV but containing basement membranes has forced a revision in this theory. Collagen IV also has great relevance to human health, as mutations in three of the six collagen IV chains can cause kidney failure and deafness. In addition, one of the chains harbors a cryptic epitope that in rare cases is attacked by the immune system, leading to kidney disease and lung hemorrhage.

Sulfated proteoglycans are widely deposited in the extracellular matrix. The chapter by Arikawa-Hirasawa provides an in depth discussion of

perlecan, the major heparan sulfate proteoglycan in basement membranes that is also found in other extracellular matrices. Perlecan binds to many matrix molecules, growth factors, and cell surface receptors and is involved in regulating angiogenesis. Mutations in perlecan are responsible for several rare human syndromes that affect muscle and skeletal development and function. Studies in mice lacking perlecan indicate important roles in heart development and potentially in development of atherosclerosis.

Abnormal matrix accumulation in atherosclerotic vessels is certainly a serious health problem. The chapter by McLean, Mecham, and colleagues deals with extracellular matrix gene expression during normal development in the mouse aorta. These authors performed gene expression profiling at different stages of aortic development and provide a comprehensive analysis of expression of pertinent matrix proteins, including collagen, elastin, fibrillin, fibronectin, laminin, and various proteoglycans. They also profile the non-matrix-related genes expressed by the vascular smooth muscle cells present in the aortic wall. These data show that vascular smooth muscle cells exhibit a wide range of phenotypes at different stages of development that may relate to their abnormal behavior in the setting of vascular disease.

The extracellular matrix associated with the dermal-epidermal junction in the skin is crucial for maintaining the barrier function of the skin and preventing blistering. The chapter by Tzu, Li, and Marinkovich discusses the specialized nature of the matrix molecules and their receptors that comprise the dermal-epidermal junction. Interactions among these proteins maintain the integrity of the linkage between dermis and epidermis. There are a number of human skin diseases caused by mutations in these matrix components and in their receptors, and most of these result in blistering that in some cases can be so severe as to be lethal. Studies of the dermal-epidermal junction have led to an overall better understanding of the mechanisms of how cells interact with their neighboring extracellular matrix.

Cell/matrix interactions have been shown by many groups to be crucial for proliferation, differentiation, and migration of neurons and glia. The chapter by Belvindrah and Müller reviews what is known about integrin signaling and development of the central nervous system. It has become clear from studies of mice lacking either integrin receptors or their ligands that interactions between these two classes of molecules literally shape the brain, as defects in foliation are apparent in the various mutants. However, this appears to be more a product of effects on cell proliferation rather than directly on cell migration.

A complex component of the nervous system that is especially difficult to access is the auditory system of the inner ear. But its location within bone has not prevented progress toward understanding the extracellular matrix molecules that are deposited in the inner ear. These proteins are known to be important in the function of sound transmission because mutations in several of them have been found to be associated with deafness in humans. The

chapter by Cosgrove and Gratton presents a detailed account of the matrix molecules expressed in the inner ear, where they are deposited, and which ones are associated with hearing loss. Mutations that affect proteins found either in connective tissue and or in basement membranes can cause impaired hearing.

Many investigators who study extracellular matrix are interested in cancer and metastasis. This is because the spread of cancer from one tissue to another requires the cancerous cells to move through one or more extracellular matrix barriers. The chapter by Zent and Pozzi concentrates on the role of extracellular matrix in the progression of cancer and how cells use matrix-degrading enzymes, primarily matrix metalloproteinases, to overcome the natural matrix barriers present in tissues. It has recently become clear that fragments of extracellular matrix proteins, which result from their cleavage by matrix-degrading enzymes, can have novel activities—both positive and negative—in regulating cancer cell migration, invasion, or recruitment of new blood vessels. Matrix components may therefore potentially be used as therapeutic tools for the treatment and prevention of cancer.

So if you are a reader who needed convincing that extracellular matrix proteins are not boring, I trust that this brief introduction has accomplished that. If you were already somewhat familiar with the activities and importance of extracellular matrix proteins in development and disease, I trust that this brief introduction has made it clear that there is so much more to learn and discover about these very interesting proteins.

JEFFREY H. MINER, Ph.D
Washington University School of Medicine