

Preface to the Series

The first volume of the *Biology of Extracellular Matrix* series was published in 1986 and was titled “Regulation of Matrix Accumulation.” Twelve volumes in the series were published over a period of 12 years and each volume provided timely reviews on current topics of ECM biology. With the contraction of the publishing industry in the late 1990s, Academic Press, the former Series publisher, was purchased by Elsevier and they decided to discontinue most of their monograph series, including the *Biology of Extracellular Matrix*. I was able to retain the rights to the series title and was pleased when Springer agreed to resume publication. The volume “The Extracellular Matrix: An Overview,” Robert P. Mecham (Editor), is the first under the new publisher. It should also be noted that the series is being published in collaboration with the American Society for Matrix Biology.

The Study of Extracellular Matrix Biology

Over the years, our understanding of extracellular matrix (ECM) function has evolved from the early concept of a static “connective tissue” that ties everything together to one of a dynamic biomaterial that provides strength and elasticity, interacts with cell-surface receptors, and controls the availability of growth factors. There is now no question that ECM is an important part of cell biology, and to understand cellular differentiation, tissue development, and tissue remodeling requires an in-depth consideration of the ECM components that are produced by the cell. As we look back through the relatively short history of ECM biology, we find that the field was first dominated by biochemistry (mostly chemistry!) where investigators were trying to isolate and identify the individual ECM components. The proteins that were identified were, indeed, unique in their structure, composition, and function and were unlike other proteins in living cells. The ECM is designed to function as homo- and heteropolymers that are generally insoluble in their mature state. They also have relatively long half-lives compared with other proteins in the body. Some contain unique cross-links, some have high amounts of

sulfated polysaccharides, some are designed to be “sticky” in terms of interacting with cells, and others form complex adhesion surfaces and diffusion barriers between different cell layers. In all cases, however, each class of ECM molecule is designed to interact with another to produce the unique physical and signaling properties that support tissue structure, growth, and function.

This brings us to the field today, where the tools of cell and molecular biology together with the power of model organism genetics allow us to focus on the functional complexities of the ECM biopolymer. Constructing a complex, mechanically appropriate matrix requires the cell to know the instructions for assembly, to have knowledge of the available building materials, and be able to interpret information about the stresses that the final material will have to endure. In this regard, it is clear that cells are adept at reading the instructive signals from the microenvironment, and changing the mix of matrix proteins needs to be added at any particular instance. While there is still a need to use biochemistry to characterize the individual ECM components, to fully understand the ECM requires a fundamental knowledge of cell biology. We need to understand, for example, the cellular mechanisms that lead to coordinated expression, both temporally and spatially, of complex sets of genes that encode ECM proteins as well as the enzymes responsible for their secretion and assembly. Building a functional collagen fiber, for example, involves activating and regulating genes for collagen alpha chains, hydroxylating enzymes, proteases to process propeptide regions, lysyl oxidases for cross-linking, and other chaperones and assembly proteins. Similar complexities are involved in the processing and assembly of most ECM networks, including basement membranes, elastic fibers, and large proteoglycan matrices. Virtually, all fields of animal and plant biology are concerned with questions of extracellular matrix in some manner. It is my hope that this series will prove helpful to all those seeking an introduction to EMC biology as well as experienced ECM investigators who are interested in greater insight into ECM function. In the preface to volume one of this series over 2 decades ago, I pointed out that the series cannot thrive without a large measure of enthusiasm and active participation from the ECM community. I welcome your suggestions of topics for future volumes and look forward to your feedback as we explore the extracellular matrix.

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Preface to the Volume

The objective of this overview volume in the “Biology of Extracellular Matrix” series is to update and build upon topics discussed in previous volumes in this series as well as in classic ECM review texts, such as Betty Hay’s *Cell Biology of Extracellular Matrix*. The first chapter by Jürgen Engel and Matthias Chiquet is the ideal introduction to ECM biology. It provides an overview of ECM structure and function in a creative and insightful interpretation of the ECM as a complex “machine.” The authors outline the basic features of the major classes of ECM components and describe how their multidomain structure allows multiple functions to be combined in one, often large molecule that is engineered to undergo multimeric assembly and extended multimolecular networks. They show how ECM components together with their cell surface receptors can be viewed as intricate nanodevices that allow cells to physically organize their 3D environment, as well as to sense and respond to various types of mechanical stress. They also make the point that metazoan evolution would not have been possible without the concomitant expansion of ECM complexity. Using examples of phylogenetically “old” versus “young” ECM protein families, they review the evidence that today’s incredible diversity of ECM components arose from the recombination of preexisting protein modules by exon shuffling during evolution.

The second chapter focuses on fibronectin and other glycoproteins that mediate cell adhesion through interactions with integrins. Jieli Xu and Deane Mosher use an in-depth analysis of fibronectin as a prototype to illustrate how the domain organization of adhesive glycoproteins is structured to bridge interactions between cells (integrin binding domains) and other components of the ECM, including collagen, heparan, and fibrin. They also discuss fibronectin assembly and the importance of integrins and the cellular cytoskeleton in this process. Other glycoproteins discussed in this chapter include vitronectin, the laminins, thrombospondins, tenascins, entactins, nephronectin, and fibrinogen. A short section on integrin signaling is also included.

Of all of the ECM proteins, few are as old as collagen. In early parazoa (like sponges), cells are embedded in an ECM consisting mainly of fibrillar collagens not

unlike those of higher animals. In Chap. 3, David Birk and Peter Brückner bring us up-to-date on collagen types and collagen fibril assembly. There are 28 different types of collagen in vertebrates (many more in invertebrates) that assemble into a variety of supramolecular structures including fibrils, microfibrils, and network-like structures. This chapter begins with a general discussion of collagen molecules and their supramolecular structure, assembly, and function within extracellular matrices. One of the more interesting aspects of collagen biology as outlined in this chapter is the description of mechanistic principles involved in the assembly of collagen-containing suprastructures. This includes the characterization of tissue-specific collagen fibrillogenesis, which serves to generate the diversity in extracellular matrix structures and functions required for individual tissue function.

As multicellular organisms evolved and grew more complex, there arose a need during development to separate polarized epithelial cells from underlying mesenchymal cells. This separation process, i.e., gastrulation, would not be possible without the appearance of the basement membrane – a unique ECM structure that combines the structural rigidity and unique basket-weave-forming properties of collagen type IV with cell-adhesive proteins (e.g., laminins) and charged proteoglycans (e.g., perlecan and agrin). The chapter on basement membranes by Jeffrey Miner summarizes our current knowledge about the basement membrane components and their receptors on cells. Basement membrane assembly is also discussed along with a number of human genetic diseases caused by mutations that affect basement membrane components.

The discussion of proteoglycans is separated into two chapters. The first, Chap. 5, authored by Thomas Wight, Bryan Toole, and Vincent Hascall, focuses on hyaluronan and the large aggregating proteoglycans. This family includes aggrecan, versican, neurocan, and brevican. These proteoglycans form macromolecular complexes with hyaluronan and contribute to the structural and mechanical stability of different tissues. Considerable evidence suggests that the large hydrodynamic space occupied by glycosaminoglycan chains influences tissue turgidity and viscoelasticity. In addition, recent data point to a prominent role for these ECM structures in direct cell signaling as well as an ability to bind and sequester growth factors and morphogens that are important for cell movement and differentiation. The chapter also contains a description of new functions mapped to the proteoglycan core protein.

The small leucine-rich proteoglycans (SLRPs) are discussed in Chap. 6 by Renato Iozzo, Silvia Goldoni, Agnes Berendsen, and Marian Young. SLRPs serve as tissue organizers by orienting and ordering various collagenous matrices during ontogeny, wound repair, and cancer. They also interact with a number of surface receptors and growth factors thereby regulating cell behavior. The focus of this chapter is on novel conceptual and functional advances in our understanding of SLRP biology with special emphasis on genetic diseases, cancer growth, fibrosis, osteoporosis, and other biological processes where these proteoglycans play a central role.

One of the newest ECM structures to be described and characterized, but among the oldest ECM structures in evolution, is the microfibril. The core elements of

these 10–15 nm filaments are the fibrillins – large cysteine-rich proteins that can be found as far back in evolution as the placozoans and, perhaps, parazoans. First described as components of elastic fibers, microfibrils are now known to be important regulators of growth factor signaling through their ability to bind and sequester growth factors, particularly TGF- β family members. In Chap. 7, Dirk Hubmacher and Dieter Reinhardt provide an overview of the structure, assembly, and functions of fibrillins and microfibrils as well as the pathobiology associated with genetic aberrations in the microfibril system.

Vertebrate evolution would not have been as successful as it was without elastin. As the name implies, elastin imparts elasticity to tissues, particularly large blood vessels and the lung. Without elastic vessels, it would not be possible to evolve an efficient closed, pulsatile circulatory system that supports efficient distal perfusion and body growth. Similarly, the mechanical function of the vertebrate lung would not be possible without elastin. Beth Kozel, Robert Mecham, and Joel Rosenbloom discuss this unique, highly cross-linked protein in Chap. 8. Emphasis is given to how the protein works as an elastomer and why damage to elastic fibers is so detrimental to tissue integrity and overall longevity. Diseases linked to mutations in the elastin gene are discussed, as are animal models of these diseases.

Collagen and elastin function is a polymer where individual chains are cross-linked one to another via modified lysine residues. The enzyme responsible for initiating the cross-linking reaction is one or more members of the lysyl oxidase family. These copper-requiring enzymes catalyze the oxidative removal of lysine epsilon-amino groups to form a reactive aldehyde, the cross-link precursor. There are five known members of this amine oxidase family (lysyl oxidase and 4 lysyl oxidase-like enzymes), and in Chap. 9, Herbert Kagan and Faina Ryfkin provide a detailed analysis of the amino oxidase mechanism of lysyl oxidase and bring us up-to-date on the known functions of the individual family members. They also review evidence showing that LOX can function both as an anti-oncogenic agent as well as an enhancer of malignancy in selected cancerous conditions.

Fibulins are a family of proteins that share a common architectural signature, namely a series of epidermal growth factor (EGF)-like modules followed by a carboxy terminal fibulin-type module. Over the last few years, the biological role of the fibulins has become clearer as new members of the family were identified and knockout mice provided insight into fibulin function. In Chap. 10, Marion Cooley and Scott Argraves review the current understanding of structure–function relationships for the fibulins, particularly with regards to elastogenesis. They also discuss the role that fibulins play in diseases such as cancer, cardiovascular disease, and eye disease.

In the final chapter of the volume (Chap. 10), David Roberts and Lester Lau provide an extensive review of a class of extracellular matrix components referred to as “matricellular proteins.” These proteins, in general, share a complex modular structure that enables them to interact with specific components of the matrix while engaging specific cell surface receptors through which they control cell behavior. Matricellular proteins, including the thrombospondins, some thrombospondin-repeat superfamily members, tenascins, SPARC, CCN proteins, and SIBLING

proteins, are increasingly recognized to play important roles in inherited disorders, responses to injury and stress, and the pathogenesis of several chronic diseases of aging.

What Is Not Included and Plans for the Future

Trying to review the entirety of extracellular matrix in one volume is an impossible task. For this reason, I have chosen to focus this first volume on the major molecules that make up the ECM. Subsequent volumes that are either in production or in the planning stages include ECM turnover, glycoprotein biology, integrins and receptors for ECM, and volumes devoted to topics such as ECM in development and the role of ECM in specific diseases. It is hoped that this “overview” volume will be used as a basis of reference as we explore ECM function more deeply in subsequent publications.

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