

# Preface

The extracellular matrix (ECM) is a simple descriptive term that belies the complex nature, variety, and versatility of the components and their interactions in this tissue compartment. Far from being a simple “space-filler” or “ground substance,” the ECM is fundamentally responsible for the structural integrity of all multicellular organisms. Selective expression and interactions between ECM components determine the architecture and physical properties of the matrix. Furthermore, both through direct receptor-mediated interactions with cells and by binding and regulating availability of potent growth factor molecules, the matrix influences cell adhesion, migration, and differentiation.

Proteins of the ECM tend to be modular and multifunctional, allowing dynamic bridging between ECM components and facilitating physical organization of tissues. Since the first appearance of these ECM proteins, many of them relatively early in metazoan evolution, there has been a great expansion in their variety and versatility including, in higher chordates and vertebrates, the introduction of “new” proteins such as fibronectin, elastin, and the microfibril-associated glycoproteins (MAGPs). This volume gathers together the current state of knowledge of the functions and interactions of these ECM proteins and their evolutionary histories and offers insights into mechanisms underlying the remarkable explosion of diversity and functionality through metazoan evolution.

In Chap. 1, Adams provides a general introduction to metazoan evolution, the appearance of the ECM as a simple “glue” between cells, and its subsequent expansion and functional diversification. She briefly reviews the function of several of the members of the ECM family of proteins and points out the importance of modularity, domain acquisition, and oligomerization for function. She also addresses the question of possible pre-metazoan origins of at least some matrix proteins.

Further details of possible mechanisms for generating diversity are addressed by Wada in Chap. 2. In particular, he focuses on evidence for exon-based domain shuffling as a mechanism for assembly of “new” matrix components, giving examples from cartilage and cell adhesion proteins. He also points out the importance of gene and genome duplication events followed by divergence of sequence and function and the possible emergence of novel motifs from noncoding genomic sequences.

In Chap. 3, Exposito and Lethias address the early metazoan origins of collagen as a simple tandem repeat sequence of Gly–Pro–Pro. They provide a model, involving sequence reduplication, exon shuffling, and rounds of genomic duplication, for the expansion of this ancestral sequence to generate the large family of collagens and collagen-like proteins now present in all invertebrates and vertebrates.

Chapter 4 provides information on the evolutionary history of elastin, an ECM protein with the unusual properties of extensibility and elastic recoil that emerged rather late in evolution, coinciding with the development of pulsatile, high-pressure, closed circuit circulatory systems in vertebrates. In this chapter, Keeley discusses sequence motifs and styles that appear to be required for such elastomeric properties, identify both domains shared by all elastins and domains that are highly variable between species, and propose a model for expansion and diversification of elastin sequences among species through multiple and differential replication of exon pairs at a specific site in the elastin gene.

In Chap. 5, Jensen et al. introduce the fibrillin family of proteins, which have ancient roots in metazoan evolution. Fibrillins are the principal component of microfibrils, distinctively beaded filaments present not only in association with elastin in elastic tissues but also independently providing structural integrity in other tissues. Indeed it has been proposed that, before the appearance of elastin, these microfibrillar filaments were responsible for extensibility and recoil in vascular and other tissues. The authors discuss the similarities in domain structure and arrangements between fibrillins and members of the latent TGF- $\beta$  binding protein (LTBP) family and review current knowledge on the organization and assembly of microfibrils and their role in regulating cell activity through binding of growth factors.

In Chap. 6, Segada describes the fibulin and MAGP families of microfibrillar-associated proteins, the former present at the base of metazoan evolution and the latter only appearing in chordates. He introduces the important concept of coevolution of a “suite of genes” within a functional module and the additional evolutionary considerations that may be a consequence of such functional linkages. He then traces the appearance of additional members of the fibulin and MAGP families through exon shuffling and gene duplication events, adding further diversity and subtlety to their range of functions, including important interactions with elastin in the formation of elastic fibers.

Chapter 7, written by Baratta et al., describes the functions and evolutionary origins of the SPARC and tenascin families of proteins. Unlike the previously considered proteins, which either form the fundamental building blocks of polymeric ECM assemblies or are integrated into these assemblies, SPARCs and tenascins function as soluble, diffusible components of the matrix. Both of these proteins have important roles in regulating signaling pathways, particularly those involved in angiogenesis and fibrosis.

In Chap. 8, Roberts and Frazier introduce the thrombospondin family of proteins, which also have origins early in metazoan evolution. They discuss the development of modularity and oligomerization and the remarkable ability of these bridging proteins to interact with a wide variety of cellular receptors as well as with other matrix components.

In Chap. 9, Johnson et al. describe the pre-metazoan origin of integrin-like cell adhesion receptors and their critical role in the increasing complexity of multicellular organisms throughout metazoan evolution. They review the earliest appearance of integrin-like domains, the diversification of their binding to both extracellular and intracellular partners, and their coevolution with other cellular and matrix components.

Several common themes emerge. These include the fundamental role of modularity in matrix proteins, both for their multiplicity and selectivity of interactions as well as for the facilitation of further diversification through processes such as exon duplication, exon shuffling, and gene and genome duplication. Overlying all of these is the recognition that the ECM consists of an integrated network of interactions, imposing additional coevolutionary constraints. While further sequence data and analyses will no doubt clarify the complexity and answer at least some of the many remaining questions, these contributions will provide the reader with an comprehensive overview of current knowledge of the origins of the remarkable functional diversity of matrix proteins.

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