Preface

Over the past few decades cell biology and biological chemistry have increasingly turned their attention to the space among cells (extracellular matrix, ECM) and revealed elaborate networks of macromolecules essential for structural support, cell migration, adhesion, and signaling. Macromolecules, such as proteoglycans and glycoproteins, collagens, laminin, fibronectin, matrix proteases, enzymes regulating glycan synthesis, and degradation are all components of ECM. Upon interactions in the extracellular space they affect ECM dynamics and via cell surface receptors and co-receptors (e.g., integrins and syndecans) communicate with the cellular compartment.

Progress in biochemical tools and the advancement of existing and the introduction of new analytical and biotechnological techniques have enabled the determination of the structural characteristics of various classes of matrix macromolecules in unprecedented detail. Studies of their biological roles using approaches from the field of cell biology helped the growth and expansion of the field of ECM biology.

ECM constituents contribute to tissue organization, development, and remodeling as well as its properties, such as elasticity and strength. Due to their unique structural features, matrix components interact with each other, with cell surface receptors, and with the various growth factors, thus regulating cell signaling and function. It is well established that they are all partners of a dynamic elaborative network that regulates cell functions and properties; that is, proliferation and apoptosis, differentiation, adhesion, and migration.

Matrix-mediated regulation of the various cell functions has been demonstrated during the past decade based on *in vitro* and *in vivo* models. Therefore, ECM molecules are essential players in physiological and pathological conditions. Mutations and structural alterations of matrix effectors are closely related to the development and progression of common diseases, such as cancer, including invasion and metastasis, cardiovascular disease, musculoskeletal disorders, inflammatory, and rarer conditions.

The number of research articles published year by year about ECM is increasing so fast that it would not be possible to cover all ECM biology within the limited space of one book. Therefore, the presentation of key aspects of ECM organization and regulation in health and disease was a great challenge for this book's editor and section editors. Our ambition was to present a comprehensive handbook of ECM, and to that direction 53 chapters were organized into an introductory chapter and seven thematic sections, giving an overview of the current state of knowledge of matrix components (structure and function), their roles in health and disease (matrix pathobiology and signaling) as well as new concepts of pharmacological targeting.

Thanks to the enthusiastic contribution of the section editors and chapter authors, *Extracellular Matrix: Pathobiology and Signaling* covers major areas of importance. Each section commences with an introduction written by the section editor, providing the reader with a short historical background, where necessary, as well as the importance of the ECM molecules and their interacting networks on cell properties and function.

Each chapter is organized as a timely review including concluding remarks/future perspectives, and a take-home message.

The section edited by Evi Heldin focuses on the field of *glycobiology* and covers within six chapters key molecules and areas, among them hyaluronan and sulfated glycosaminoglycans in cancer, inflammations, and metabolic control. In addition to giving insights into the function of glycans, this section also highlights striking differences in their biosynthetic machinery. Furthermore, their role in the diagnosis and therapeutics of various diseases is discussed.

The section edited by Liliana Schaefer comprises seven chapters that cover the major families of *proteoglycans* (aggrecan, versican, perlecan, small leucine-rich proteoglycans, syndecans, glypicans, and serglycin). It summarizes our rapidly expanding knowledge in the field of proteoglycan biology with emphasis on proteoglycans' intricate composition and multiple functions. This section particularly aims to recapitulate the newly described "dual function" of proteoglycans acting both as structural components and signaling molecules, depending on the biological context. It describes the implications of these signaling events in various diseases. Furthermore, it promotes the idea to translate our knowledge of proteoglycan signaling into novel therapeutic strategies for the treatment of malignant, inflammatory, and fibrotic diseases.

The section edited by Jan-Olof Winberg has six chapters that review various aspects of some of the most well-studied families of the main *proteases* found in the extracellular space. This section emphasizes the role of proteases and their endogenous inhibitors in tissue remodeling, wound healing, as well as their regulatory role in health and disease. Complex formation of individual matrix metalloproteinases (MMPs) with other MMPs, ECM macromolecules, non-ECM molecules, and cell surface receptors as well as the biological role of these complexes are also described. Furthermore, new techniques used to study the degradome, that is, the complete set of proteinases produced by an organism, are also described.

The section edited by Donald Gullberg is divided into five chapters dedicated to *cell surface receptors* covering integrins, syndecans, CD44, DDR, and their roles in cell signaling and pathophysiology as well as mechanical strain and TGFβ signaling. The matrix receptor section predicts an exciting future in the field of ECM receptor research, especially with regard to the contribution of these receptors to different disease mechanisms. Equipped with new methodological tools and refined analysis techniques, it is suggested that in the years to come new liaisons and mechanisms of action will be identified where matrix receptors will play both supporting as well as leading roles.

The section edited by Ruggero Tenni encompasses six chapters that describe up-to-date information on *collagens*. Emphasis is on the expanding knowledge of some basic issues on collagens themselves, their folding, maturation and morphology, and mutations in collagen alpha chains. The issues discussed are: the characteristics of trimerization domains in different collagen types; a class of proteinases, originally identified as components of procollagen processing, involved, for example, in morphogenesis and repair; a deeper understanding the effect of several factors on the phenotype in human pathologies caused by missense mutations in the triple helix of collagens, such as Osteogenesis Imperfecta; collagen I fibrils' morphology itself, which still deserve a discussion of the state of the art and of the open questions. The high degree of connectivity of collagen with "countless" ligands is also emphasized, in two chapters, by discussing the

interactome of several collagen types and by the detailed knowledge of the interaction for the few collagen ligands whose binding site in collagen is known.

The section edited by Achilleas Theocharis focuses, in its seven chapters, on the *emerging aspects in ECM pathobiology*, where the implication of certain ECM molecules, among them hyaluronidases, EMMPRIN, syndecan-1, and serglycin, in the development and progression of malignancies is discussed. A proteomic approach for studying ECM involvement in cancer as well as the utility of 3D matrix systems and new quantitative methods in studying cancer are also presented. It also exhibits the role of bone sialoprotein in skeletal infections.

The last section, which I edited, groups together a series of eight chapters dealing with novel approaches in respect to the *pharmacological targeting* at the ECM level in cancer. In particular, the importance of tumor microenvironment, targeting epithelial to mesenchymal transition at the level of protein-glycan interactions, the importance of growth factor effects in the expression of ECM molecules with possible pharmaceutical interventions, targeting shedding syndecans in cancer, fresh ideas on the proteoglycan receptors with phosphatase activity, and the importance of heparanase, a multifaceted protein in inflammation and cancer, are presented. Aspects regarding delivery systems as well as glycan analogues as therapeutic agents are also presented within the chapters.

The text and the contents of this book have been organized in such a way so as to be easily understood by researchers in distinct scientific fields; that is, biochemistry, cell and molecular biology, biotechnology, pharmacology, and medicine, in both academic and industrial sectors. We hope that this book will put forward the emerging concepts and future prospects of the field of *ECM Pathobiology and Signaling* and will also stimulate new studies in this very interesting scientific area that will provide an in-depth understanding of disease progression and treatment, and will attract new investigators in the field.

This book has been developed through the efforts of 124 well-known scientists for their achievements in the field of ECM, representing 16 countries and 4 continents. I wish to express my gratitude to all authors and section editors for their contributions, and the harmonic collaboration during all preparation steps of this book. Moreover, the contribution of my colleagues in this endeavor and particularly of Achilleas Theocharis and Chrisostomi Gialeli is greatly acknowledged. From my personal view, I feel amply rewarded learning a lot during reading and editing the chapters of this book.

I would also like to thank the editorial director, Dr. Stephanie Dawson, and the production team at de Gruyter for their contribution to the successful realization of this multisection and multiauthor book, both in a printed and electronic version (e-book).

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Editor