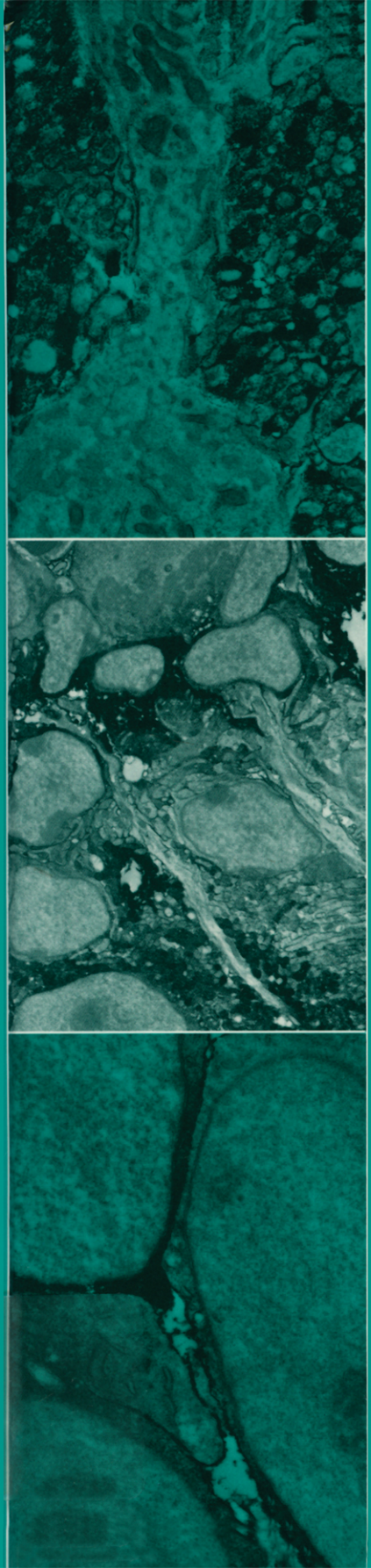

Receptors for Extracellular Matrix

EDITED BY

John A. McDonald
AND
Robert P. Mecham

Receptors for Extracellular Matrix

Biology of Extracellular Matrix Series

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RECEPTORS FOR EXTRACELLULAR MATRIX

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Front cover photograph: EM immunocytochemical localization of thrombospondin in sagittal sections of day 10 cerebellar cortex. See chapter by Reichardt and Tomaselli, Figure 4 for details. Courtesy of Dr. K. Sue O'Shea.

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Preface

Primitive multicellular organisms inhabiting primordial seas must have benefited from cellular specialization. Proof of this statement is found in the wondrous diversity of plant and animal life inhabiting our world. It might be argued that becoming specialized while retaining cell–cell connections required heterotypic as well as homotypic interactions. Cytodifferentiation and compartmentalization into tissues and organs required even greater specialization, which presumably led to the development of specialized molecules for the extracellular matrix.

The extracellular matrix has become an important area of research for almost every aspect of cell biology. Insight into how a cell responds to signals associated with the extracellular compartment requires an understanding of the components at the cell-matrix interphase that react with and interpret matrix-associated signals. A detailed understanding of the structure and function of a variety of cell-matrix receptors has been accomplished during the past years. In this volume, we have attempted to define the major receptor families, and where possible, identify potential biological functions.

The presence of cell surface proteoglycans has been evident for many years, but their role in cell-matrix interactions is still unclear. Cell surface proteoglycans interact with a variety of extracellular molecules, many of which exert an effect on cell behavior during development, invasion, and metastasis. Markku Jalkanen, Sirpa Jalkanen, and Merton Bernfield discuss the structure and function of membrane-associated proteoglycans, focusing on two classes of integral membrane molecules: Syndecan and CD44. Recent work has revealed that CD44/Hermes antigen can exist both with and without GAG chains. Both CD44 and Syndecan are members of a family of closely related molecules, which differ in the nature and extent of their glycosylation and possibly also in core protein structure.

Inherited defects in LeuCAMs or leukocyte adhesion molecules result in the disease of leukocyte adhesion deficiency, a human model of integrin-related disease. Eric J. Brown and Irene L. Graham review current knowledge concerning macrophage and inflammatory cell matrix receptors and other leukocyte integrins. They discuss the particularly important area of mechanisms of signal transduction from inte-

grin receptors, which must mediate the effects of extracellular matrices and other ligands on cell behavior.

Peter End and Jürgen Engel review multidomain proteins of the extracellular matrix and their role in controlling cellular growth, a relatively new area of cell matrix interaction under active investigation. It is important to recognize that the growth of cells during development, differentiation, and wound repair is not just under the control of small soluble growth factors and cytokines, but also appears to be under regulation by extracellular matrix components. Domains on these matrix components may in some cases actually occupy growth factor receptors, or alternatively, may transmit information via a distinct set of receptors such as integrins, which effect cell growth through unknown mechanisms.

Urs S. Rutishauser reviews the voluminous literature on NCAM, the most abundant and widespread of the known vertebrate cell–cell adhesion molecules. He particularly emphasizes the role of posttranslational glycosylation with polysialic acid in the function of the NCAM molecule, which undergoes unusual and highly characteristic differences in glycosylation during development, illustrating one strategy by which the biological activity of cell surface receptors is modulated.

Louis F. Reichardt and Kevin J. Tomaselli review the recent literature on the regulation of neural development by the extracellular matrix. Cells of the central and peripheral nervous system face formidable strategic difficulties, including the necessity for exquisitely guided migrations over very long distances, remarkable patterns of cytodifferentiation, and the ability to reinnervate target tissues after injury. It is not surprising that extracellular matrices and matrix receptors play key roles in all of these events, and that the authors' laboratory has been at the forefront of investigations in this area.

Martin J. Humphries, A. Paul Mould, and Kenneth M. Yamada review the molecular basis of cell adhesion in general, focusing on the interactions of adhesion receptors with well-characterized cellular recognition sites and extracellular ligands. This overview introduces specific examples of cell migration, including that occurring during embryogenesis, gastrulation, neural crest cell migration, neurite extension, lymphocyte migration, and wound healing, all rapidly growing areas of tumor cell biology in which the authors have played important roles.

Martin E. Hemler, a pioneer in the rapidly growing area of integrin biology, provides a cohesive and broadly based overview of the integrin family. He attempts to clarify the bewildering array of integrin associations, their physiologic relevance, and structural aspects.

Finally, Klaus von der Mark and his co-workers review the current literature on Anchorin CII, a collagen-binding protein of the calpactin-lipocortin family.

John A. McDonald
Robert P. Mecham

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Binding of Extracellular Effector Molecules by Cell Surface Proteoglycans

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and Merton Bernfield‡

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I. Introduction

A. *The Cell Surface Mediates Information Transfer*

A cell must constantly monitor molecular information from its outside to maintain itself while its environment changes. This monitoring of the extracellular environment is integrated among many cells when,

as in a functional tissue, the coordinated action of cell groups is involved. The cell surface performs the primary monitoring function; it ensures an appropriate barrier toward various compounds, such as ions or small organic molecules, and initiates the response to effector molecules in the environment, for example, soluble growth factors or insoluble matrix components. For these activities, cells have a great variety of cell surface molecules; one class of these is the cell surface proteoglycans.

The presence of cell surface proteoglycans has been evident for two decades (Kraemer, 1971), and they exist on all adherent vertebrate cells, but their role in cell behavior is still unclear. Cell surface proteoglycans interact with a variety of extracellular molecules, many of which exert an effect on cell behavior during development, invasion, and metastasis. In this review we attempt to explore these interactions by analyzing the role of cell surface proteoglycans in the binding of extracellular effector molecules.

B. Cell Surface Proteoglycans

Cell surface proteoglycans are the most anionic components of the cell surface. Their anonic nature resides in the sulfate and carboxyl moieties of their glycosaminoglycan (GAG) chains. Variations in sugars, in size, and in sulfation patterns of the constituent GAG chains can generate a wide array of molecular species, especially for heparan sulfate proteoglycans (Scott, 1988; Gallagher, 1989). Alterations in GAG structure among cell surface proteoglycans suggest that distinct proteoglycans may have specific functions in extracellular matrix organization, cellular interactions, or growth regulation.

Proteoglycans reside at the cell surface via at least three modes of attachment. Some are peripheral components that bind to the plasma membrane and can be removed from it without destroying the membrane. For example, hyaluronic acid, a GAG that does not contain a core protein (Gallagher, 1989), is commonly found at the surface of a variety of cells. Recent work with its cell surface receptor has revealed that CD44/Hermes antigen (described later in detail in this review) can bind hyaluronate to the cell surface (Aruffo *et al.*, 1990). Heparan sulfate proteoglycans can be found in a salt-extractable form at the surface of hepatocytes; a heparan sulfate-binding molecule has been proposed to mediate this binding to the cell surface (Höök *et al.*, 1984). An integral membrane protein binds the core protein of a basement membrane heparan sulfate proteoglycan to the cell surface (Clement *et al.*, 1989).

Cells also contain integral membrane proteoglycans that can be removed only by disrupting the plasma membrane. These proteoglycans

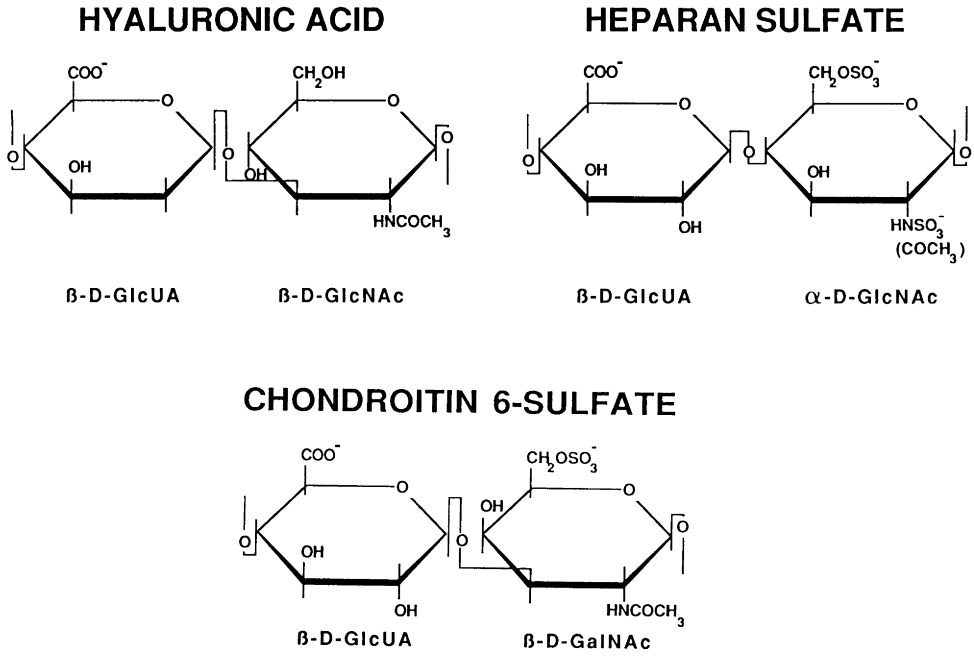

FIG. 1. Schematic structures of disaccharides of cell surface glycosaminoglycans. Each disaccharide is repeated in a linear polymer. Hyaluronan is included for comparison. Chondroitin sulfates can contain 4- or 6-sulfated disaccharides. Dermatan sulfate is a type of chondroitin 4-sulfate that has frequent replacement of the D-glucuronate with L-iduronate. Heparan sulfate and heparin share the same disaccharide structure, but heparin is more extensively O-sulfated and heparan sulfate is more extensively N-acetylated and these are frequently repeated in tandem arrays.

are intercalated into the plasma membrane via a hydrophobic transmembrane protein domain (Saunders *et al.*, 1989; Marynen *et al.*, 1989) or are covalently linked to membrane phospholipid (Carey and Evans, 1989; David *et al.*, 1991). These represent a class of molecules, integral membrane proteoglycans, and our review focuses on two well-characterized examples. The first, syndecan (Saunders *et al.*, 1989), exists only as a proteoglycan, but the second, CD44 (Goldstein *et al.*, 1989; Stamenkovic *et al.*, 1989), is a so-called part-time proteoglycan, existing both with and without GAG chains (S. Jalkanen *et al.*, 1988). Both of these molecules represent a family of closely related molecules that differ in the nature and extent of their glycosylation and, possibly, in core protein structure. Indeed, other cell surface proteoglycans show marked differences in extent of glycosylation, such as the part-time proteoglycans invariant chain (Sant *et al.*, 1988), TGF-β-binding