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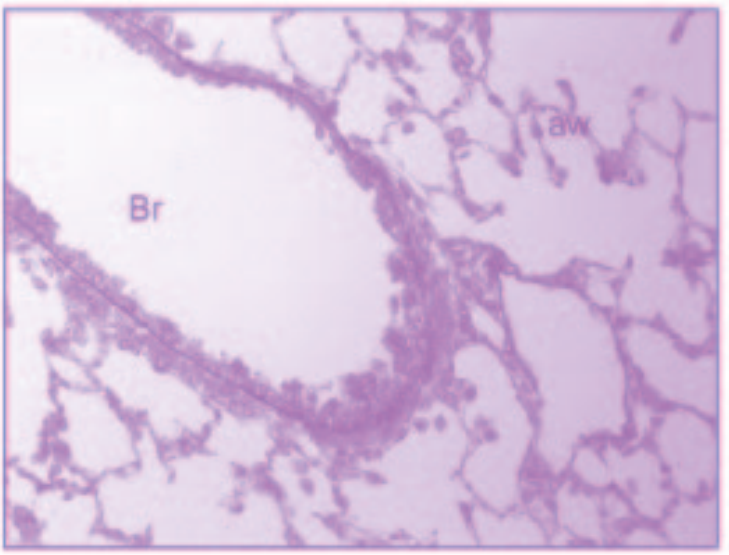
Proteoglycans in Lung Disease



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PROTEOGLYCANS IN LUNG DISEASE

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To my wife, Mithlesh
H. G. G.

To my wife, Sheila
P. J. R.

To my wife, Mary Ann
C. A. H.

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INTRODUCTION

Proteoglycans are critical to the architecture of the lung (and other tissues). All the same, these molecules are, if not ignored, at least not always at the forefront of our thinking! During the last 30 to 40 years, we have come to recognize the complex structure of the lung, as well as the interaction between the unique cells that characterize this organ and the matrix that binds these cells. The proteoglycans are, quite simply, part of the scaffolding that holds together all the pieces of this complex structure.

Proteoglycans are not unique to the lungs. We find them in cartilage, kidney, small intestine, and many—indeed, almost all—other tissues. Because of the diversity of their location, proteoglycans quite naturally come in a variety of different types.

Proteoglycans contain glycosaminoglycan chains including heparin and hyaluronan. As the editors of this monograph point out in their Preface, the interest in hyaluronan began more than 60 years ago. Likewise, heparin was identified many decades ago. However, the interactions of these molecules, and their role in the lung matrix, were not of intense research interest until recently. This is surprising when one considers that for years heparin was mostly extracted from lung tissue.

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In 1976, Dr. R. G. Crystal, editor of *Biochemical Basis of Pulmonary Function*, Volume 2 of the Lung Biology in Health and Disease series, included a chapter titled ''Proteoglycans and Elastic Fibers.'' Then, in 1989, Dr. D. Massaro, editor of *Lung Cell Biology*, Volume 41 of the series, presented an update titled ''Proteoglycans of the Lung.'' This ever-increasing interest in the proteoglycans underscores their importance in the biology of the lung's extracellular matrix, the scaffolding, and the structural and functional development and integrity of the lung in health and disease.

This volume, *Proteoglycans in Lung Disease*, edited by Drs. H. G. Garg, P. J. Roughley, and C. A. Hales, represents the interest in this field of proteoglycans as it relates to the lung. It is presented by a cadre of scientists whose expertise ranges from fundamental biology to the clinical relevance of these molecules. In addition, and just as important, the authors provide the readers with a detailed panoramic review of the role the proteoglycans play in biology and in lung pathology. As stated by the editors, the content of this volume is a step toward the ultimate goal to provide new therapeutic targets.

As the Executive Editor of the Lung Biology In Health and Disease series, I am as proud to introduce this volume as I am grateful to its contributors for the opportunity to do so.

Claude Lenfant, M.D.
Bethesda, Maryland

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PREFACE

During breathing, the lung undergoes a constant change in volume. This function places special demands on the pulmonary connective tissue skeleton, particularly lung alveoli, where the gas exchange process takes place. For efficient functioning of the lung, the walls of the alveoli should be: (a) thin, to obtain proper gas exchange, (b) firm, to prevent the collapse of the alveolus, and (c) flexible, to cope with expansion during breathing.

The extracellular matrix maintains the functions of the lung by supporting its architecture that contains proteoglycans, collagens, and noncollagenous proteins. In normal tissue a balance is maintained between synthesis and degradation of proteoglycans, and this balance is disturbed by either injury or disease. Many lung diseases are amenable to correction or cure whereas others, such as adult respiratory distress syndrome, are killers.

Proteoglycans are complex macromolecules having polysaccharide chains that are called glycosaminoglycans (GAGs). These are unbranched polymers of repeating disaccharide units that are highly negatively charged due to the presence of carboxylate and sulfate groups on their sugar residue. Most GAGs are covalently linked via a tetrasaccharide to a protein backbone, but hyaluronan is an exception, being neither sulfated nor linked to protein as part of a proteoglycan. All types of glycosaminoglycans—hyaluronan, chondroitin 4–sulfate, chon-

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droitin 6–sulfate, dermatan sulfate, heparin, heparan sulfate, and keratan sulfate—are found in the lung.

Hyaluronan was first implicated in a lung disorder about 60 years ago. This finding stimulated interest in the biological role of hyaluronan and other proteoglycans in lung diseases. Intense research efforts in the past 20 years have clearly shown that hyaluronan and proteoglycan macromolecules become altered in diseased states. The exact role of proteoglycan in lung diseases is not yet known. This book presents 18 chapters describing lung proteoglycans and the alteration of their metabolism in different diseases.

Chapter 1 focuses on the chemistry and functions of these macromolecules. Chapter 2 provides an overview of hyaluronan in lung function. Proteoglycans in an organ can be studied using biochemical and/or morphological techniques. Chapter 3 discusses these methods and their sensitivity.

The side chains of proteoglycans are highly hydrophilic, and therefore have the ability to attract ions and fluid into the matrix. This property affects tissue viscoelasticity. Lung tissue viscoelasticity has also been attributed to the movement of fibers within the connective tissue matrix. Chapter 4 discusses the effect of mechanical strain on the distribution and properties of lung proteoglycans.

Maintenance of a normal extracellular matrix is essential for the function of a normal lung. Changes in hyaluronan occur during development. Chapter 5 discusses hyaluronan and how its binding proteins occur in relation to lung biology during development and in response to a variety of insults. Chapter 6 reviews the currently known intracellular signaling pathways activated after hyaluronan interacts with its receptors.

Pleural mesothelioma is an uncommon complication of asbestos exposure, originating from mesothelial cells of pleura, peritoneum, or tunica vaginalis testis. Chapter 7 discusses the importance of hyaluronan alterations in malignant mesothelioma.

Within a relatively short period of time after birth, the lung changes from a liquid-filled to an air-filled dry organ. This is almost opposite to what is experienced during edema development. Chapter 8 describes the role of matrix proteoglycans in development of pulmonary edema.

Small proteoglycans are important during remodeling of the lung in physiological as well as pathophysiological conditions due to their effects on matrix maintenance and on cell and cytokine activities. Therefore, they are deeply involved in disease processes such as inflammation associated with fibrosis. Chapter 9 focuses on the role of small proteoglycans in the formation of fibrosis. Chapter 10 discusses the role of versican in the cell biology of pulmonary fibrosis, and Chapter 11 reviews the role of decorin in the structural remodeling of chronic asthma.

Emphysema is a condition of the lung characterized by abnormal permanent enlargement of the air spaces distal to the terminal bronchioles, accompanied by

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destruction of their walls and without obvious fibrosis. Chapter 12 summarizes the role of proteoglycans in the development and pathogenesis of emphysema.

One of the main functions of bronchial mucus is to protect the lung from airborne particles by trapping them and facilitating their clearance by ciliary movement. Chapter 13 describes proteoglycans in normal and pathological bronchial mucus.

In blood vessels, proteoglycans constitute only a minor component but are critically involved in a variety of physiological events that occur within the vascular wall. Chapter 14 focuses on the importance of vascular proteoglycans.

Bronchiectasis refers to the pathological lung condition in which the walls of medium-sized bronchi are damaged and then dilated. Chapter 15 discusses the degradation of lung matrix proteoglycans in bronchiectasis.

Hypoxia is associated with interstitial lung diseases, including pulmonary hypertension, aggressive tumor progression, and fibrosis. The relative proportions of collagen and proteoglycan reflect the type of lung disease. Chapter 16 reviews the effect of hypoxia on glycosaminoglycan synthesis by lung cells.

Understanding of proteoglycan interaction in the lung will undoubtedly lead to a better comprehension of disease pathogenesis and may provide new therapeutic targets. Chapter 17 addresses the relationship among integrins, proteoglycans, and lung diseases.

Because vascular remodeling with smooth muscle cell hypertrophy and hyperplasia contributes to the high pulmonary vascular resistance seen in primary and secondary pulmonary hypertension, interest continues in possible therapeutic agents to reverse vascular remodeling. Chapter 18 describes in detail the chemical structural modification of the glycosaminoglycan heparin in order to develop heparin derivatives as a potential therapeutic agent to reverse vascular remodeling.

In summary, this book presents significant information concerning the participation of proteoglycans in different lung diseases, with the ultimate goal of providing therapeutic targets. This book offers an overview for pulmonologists of the specific roles of proteoglycans in lung pathology. It also gives medical students and nonspecialist researchers in the pulmonary field up-to-date information on the structure and metabolism of proteoglycans and their role in the normal and diseased lung.

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