Preface

Carbohydrates are a major component of the extracellular matrix (ECM) where they associate with proteins to form glycoproteins or proteoglycans, or exist as long-chain disaccharides (e.g., hyaluronic acid). All ECM proteins except elastin have associated sugar, and, in some cases, ECM proteins require proper glycosylation to achieve full biological activity. It is also now clear that many ECM proteins have carbohydrate-binding domains that specifically recognize and interact with glycoconjugates on other matrix components and on the cell surface. Carbohydrates have been implicated in a wide variety of processes, ranging from cell adhesion and migration to matrix assembly, growth factor sequestration and regulation, involvement in many aspects of immune function, binding of plasma proteins, and control of thrombogenesis. Proteoglycans and other glycoconjugates were reviewed in earlier volumes in this series (*Cell Surface and Extracellular Glycoconjugates: Structure and Function*, David D. Roberts and Robert P. Mecham, editors; and *Biology of Proteoglycans*, Thomas N. Wight and Robert P. Mecham, editors). This volume reviews the most recent findings on the role of glycans in the development of diseases and the possible therapeutic use of this class of molecules. It shows how the interaction of glycans with growth factors, growth factor-binding proteins, extracellular proteases, protease inhibitors, chemokines, morphogens, and adhesive proteins regulates inflammation, infection, cancer, atherosclerosis, thrombosis, and embryonic stem cell biology. Further, an extensive survey of the structure and pharmacological effects of unique marine GAGs, and also the possibility to use these glycans as therapeutic agents are discussed.

Heparan sulfate is a linear polysaccharide composed of glucosamine and uronic acid (glucuronic acid or iduronic acid) disaccharide repeats with various types of sulfation modifications. In tissues, heparan sulfate covalently attaches to core proteins to form heparan sulfate proteoglycans (HSPG), and are abundant at the cell surface and in the ECM. In Chap. 1, Wang reviews our current understanding of the cellular and molecular mechanisms of heparan sulfate in the regulation of inflammation and angiogenesis. This chapter focuses on the regulatory roles of heparan sulfate on key inflammatory molecules and on the vascular endothelial

growth factor (VEGF), the master proangiogenic factor of angiogenesis. For most intracellular pathogens, cell surface HSPGs serve as a scaffold that facilitates the interaction of microbes with secondary receptors that mediate host cell entry. Consistent with this mechanism, addition of heparan sulfate (HS) or its pharmaceutical functional mimic, heparin, inhibits microbial attachment and entry into cultured host cells, and HS-binding pathogens can no longer attach or enter cultured host cells whose HS expression has been reduced by enzymatic treatment or chemical mutagenesis. In Chap. 2, Bartlett and Park provide a mechanistic overview of our current understanding of how certain microbial pathogens subvert HSPGs to promote their infection, using specific HSPG-pathogen interactions as representative examples.

Alteration in cellular glycosylation is a common phenotypic change associated with malignant transformation and cancer progression. Cell surface oligosaccharides carried on glycoproteins and glycolipids mediate communication among cells and facilitate cell adhesion, processes that are central during cancer progression. Accumulating evidence indicates that glycans contribute to tumor invasion, metastasis, and angiogenesis. Borsig (Chap. 3) provides an overview on cancer-specific changes of glycosylation on *O*- and *N*-glycans, with the focus on the function of these oligosaccharides in cancer progression.

Chapter 4 by Vicente, Godoy and Werneck focuses on the roles of different GAGs located in the vessel wall in the pathogenesis of atherosclerosis and thrombosis. GAGs in atherosclerosis can help to regulate atherogenesis through their ability to retain lipoproteins in the vessel wall. Prolonged retention of lipoproteins may render them susceptible to chemical modifications, leading to their aggregation, cellular uptake, and lipid accumulation. GAGs can also act as anticoagulant molecules because of their ability to interact with anticoagulant proteins like antithrombin and heparin cofactor II, promoting their activation and increasing their ability to inhibit thrombin.

In Chap. 5, we return to heparan sulfate where Pickford, Holley, Meade, and Merry discuss the role of this important glycoconjugate in early development. Mouse embryonic stem (ES) cells produce a poorly sulfated HS that may protect from prodifferentiation cues (e.g., fibroblast growth factors), and HS epitopes can identify cells with hemangioblast potential. Therefore, HS-sequences can identify functionally unique populations of cells and so have potential applications in the development of cell-replacement therapies for degenerative conditions. How HS chains influence differentiation events is unclear, but possible mechanisms include interactions of heparan with cytokines and chemokines. Indeed, a well-known function of HS is its ability to serve as a coreceptor to modulate cell growth, survival, and movement. These functions become relevant to heparan's role in disease as well as development. In Chap. 6, Gassar, Ibrahim, and Götte discuss the role of HS in tumor progression and cancer therapy. As matrix receptors, HSPGs act in concert with integrins to regulate tumor cell motility. As binding partners for matrix metalloproteinases and protease inhibitors, they regulate the proteolytic microenvironment of tumors, thus modulating metastatic spread. The development of glycan-based drugs targeting these biological functions has become

an area of intense research in cancer biology. This chapter discusses some of the promising results that have been obtained both in animal models and in clinical trials.

The final chapter by Kozlowski, Gomes, Silva, Pereira, Silva, and Pavão focuses on the interesting sulfated GAGs present on marine organisms. These glycoconjugates possess pharmacological properties ranging from anticoagulant and antithrombotic to antimetastatic and anti-inflammatory. In this chapter, the authors review the phylogenetic distribution, the structure, and the biological effects of the marine GAGs, as well as the molecular mechanisms involved in some of their biological activities. The possibility to use these glycans as therapeutic agents is also discussed.

It is hoped that the information in this volume will provide useful information to the research community about the broad range of functions associated with glycoconjugates in the context of development and disease. This field is especially exciting to follow because it impacts basic, applied, and clinical aspects of biomedical research. It is clear that additional practical applications will be forthcoming with advances in our basic knowledge of glycans in disease.

Rio de Janeiro, Brazil Mauro S.G. Pavão